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Acute renal failure in critically ill patients

With special reference to prediction of outcome

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Academic dissertation

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ABSTRACT

Aims: Outcome of critically ill patients with acute renal failure (ARF) and factors related to outcome were evaluated.

Patients and methods: A total of 1662 patients from two intensive care units (ICUs) and one acute dialysis unit in Helsinki University Hospital were included in the study. The patients were treated in 1998-2005.

Study I was a prospective study that included 668 consecutive patients treated in two ICUs within a period of 11 months. The prevalence of ARF was calculated and classified according to two ARF-specific scoring methods, the RIFLE (Risk, Injury, Failure, Loss of renal function, and End-stage renal disease) consensus classification and the classification created by Bellomo et al. (2001). Bellomo scores classify ARF to three categories: acute renal injury (ARI), acute renal failure syndrome (ARFS), and severe acute renal failure syndrome (SARFS).

Study II was a prospective cohort study evaluating human histo-compatibility leukocyte antigen-DR (HLA-DR) expression and plasma levels of one proinflammatory (interleukin (IL) 6) and two anti-inflammatory (IL-8 and IL-10) cytokines in predicting survival of ARF patients among 103 critically ill systemic inflammatory response syndrome (SIRS) patients treated in 1998-1999.

Study III was a prospective cohort study evaluating serum cystatin C as a marker of renal function in ARF and its power in predicting survival of ARF patients among 199 consecutive ICU patients (202 treatment episodes) over a period of nine months in 2003.

Study IV was a prospective, randomized, and controlled cross-over study. Sixteen rhabdomyolysis patients with plasma myoglobin concentrations over 10 000 µg/L were allocated into two treatment groups. Patients were treated with forced alkaline diuresis (FAD) and hemodiafiltration (HDF). Group A received HDF during hours 0-4 and group B during hours 4-8.

Study V was a cross-sectional cohort study assessing long-term survival and health-related quality of life (HRQoL) in 703 patients, who had received renal replacement therapy (RRT) for ARF during 1998-2002.

Main results: In Study I, Admission Sequential Organ Failure Assessment (SOFA) score and maximum RIFLE score for the first three days in the ICU were independent predictors of hospital mortality. The discriminative powers for hospital mortality of RIFLE and Bellomo scores as areas under curve (AUCs) were 0.653 and 0.587, respectively.

In Study II, ARF patients showed significantly lower HLA-DR expression and higher plasma levels of IL-6, IL-8, and IL-10 than nonARF patients. Moderate discriminative power in predicting survival was observed for day 2 IL-6 and IL-10 plasma levels: AUCs 0.703 and 0.749, respectively.

In Study III, excellent predictive power in the prediction of ARF for days 1-3 serum cystatin C was found (AUCs 0.885, 0.893, and 0.901, respectively), but poor predictive power in the prediction of mortality. Independent

predictors of hospital mortality were diagnosis of ARF, admission APACHE II score, and admission plasma creatinine level.

In Study IV, the decrease in plasma myoglobin during HDF and FAD was significantly greater that during FAD alone (28% vs. 14%). The mean difference in myoglobin clearances between the treatments was 6085µg/L. The mean total amount of filtrated myoglobin at the end of HDF was 58.4 mg.

In Study V, the mortality rate of ARF patients was 41% for 28 days, 57% for one year, and 70% for 5 years. Increasing SOFA score, increasing age, and need for continuous RRT were independent predictors of one-year mortality. The HRQoL, measured by the EuroQol (EQ)-5D score, was significantly lower in the study population than in the age- and gender-matched general population (0.68 vs. 0.86).

Conclusions: Based on these results, neither of the ARF-specific scoring methods presented good discriminative power regarding hospital mortality. The maximum RIFLE score for the first three days in the ICU was an independent predictor of hospital mortality.

As a marker of renal dysfunction, serum cystatin C failed to show benefit compared with plasma creatinine in detecting ARF or predicting patient survival. Neither cystatin C nor plasma concentrations of IL-6, IL-8, and IL-10, nor monocyte HLA-DR expression are clinically useful in predicting mortality in ARF patients.

HDF may be used to clear myoglobin from plasma in rhabdomyolysis, especially if the alkalization of diuresis does not succeed.

The long-term survival of patients with ARF was found to be poor. The HRQoL of those who survive is lower than that of the age- and gender-matched general population.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Åhlström A, Kuitunen A, Peltonen S, Hynninen M, Tallgren M, Aaltonen J, Pettilä V. Comparison of 2 acute renal failure severity scores to general scoring systems in the critically ill. American Journal of Kidney Diseases 48: 262-268, 2006.

II Åhlström A, Hynninen M, Tallgren M, Kuusela P, Valtonen M, Orko R, Siitonen S, Takkunen O, Pettilä V. Predictive value of interleukins 6, 8 and 10, and low HLA-DR expression in acute renal failure. Clinical Nephrology 61: 103-110, 2004.

III Åhlström A, Tallgren M, Peltonen S, Pettilä V. Evolution and predictive power of serum cystatin C in acute renal failure. Clinical Nephrology 62: 344-350, 2004.

IV Peltonen SM, Åhlström A, Kylävainio V, Honkanen E, Pettilä V. The effect of combining intermittent hemodiafiltration with forced alkaline diuresis on plasma myoglobin in rhabdomyolysis. 2006, submitted.

V Åhlström A, Tallgren M, Peltonen S, Räsänen P, Pettilä V. Survival and quality of life of patients requiring acute renal replacement therapy. Intensive Care Medicine 31: 1222-1228, 2005.

These publications are referred to in the text by their Roman numerals, and are reprinted with the kind permission of their copyright holders. In addition, some unpublished material is presented.

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ADQI	Acute Dialysis Quality Initiative
ANOVA	Analysis of variance
ANP	Atrial natriuretic peptide
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
ARFS	Acute renal failure syndrome
ARI	Acute renal injury
ATN	Acute tubular necrosis
ATP	Adenosine triphosphate
AUC	Area under curve
CAVH	Continuous arteriovenous hemofiltration
CRRT	Continuous renal replacement therapy
CVP	Central venous pressure
CVVH	Continuous venovenous hemofiltration
CVVHDF	Continuous venovenous hemodiafiltration
EQ-5D	EuroQol five dimensions
FAD	Forced alkaline diuresis
GFR	Glomerular filtration rate
HDF	Hemodiafiltration
HES	Hydroxyethyl starch
HLA-DR	Human histocompatibility leukocyte antigen-DR
HRQoL	Health-related quality of life
ICU	Intensive care unit
IL	Interleukin
LR	Likelihood ratio
MDRD	Modification of Diet in Renal Disease
NAC	N-acetylcysteine
NS	Not significant
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
QALY	Quality-adjusted life-years
ROC	Receiver operating characteristic
RRT	Renal replacement therapy
SARFS	Severe acute renal failure syndrome
SCr	Serum creatinine concentration (μmol/L) (→mg/dL, divide by 88.4)
SE	Standard error
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
TNF	Tumor necrosis factor
VAS	Visual analog scale

1. INTRODUCTION

Acute renal failure (ARF) is a clinical syndrome characterized by rapidly decreasing glomerular filtration rate (GFR), which results in disturbances in electrolyte- and acid-base homeostasis, derangement of extracellular fluid volume, and retention of nitrogenous waste products, and is often associated with decreased urine output (Nissenson 1998). ARF is a significant problem, affecting about 5% of all hospitalized patients (Hou et al. 1983) and about 5-25% of patients admitted to intensive care units (ICUs) (de Mendonca et al. 2000; Uchino et al. 2005). ARF is linked to high mortality and morbidity rates (Groeneveld et al. 1991). While comorbidities contribute to the high mortality rate (Biesenbach et al. 1992), ARF also independently increases morbidity and mortality (Levy et al. 1996).

Although ARF as a clinical syndrome is well known, no universally accepted definition exists. Commonly used definitions, as reviewed by Thadhani et al. (1996), include an increase in plasma creatinine of 44 μmol/L or of more than 50% over the baseline value, a reduction in creatinine clearance of 50%, and a decrease in renal function that results in the need for renal replacement therapy (RRT). The lack of a universal definition for ARF complicates comparison of study results for prediction, treatment, and outcome of ARF.

The etiology of ARF is often multifactorial. The most common cause of renal ARF is ischemia, leading to acute tubular necrosis (Thadhani et al. 1996). Increasing evidence exists for the role of inflammatory mediators in the pathogenesis of ischemic ARF. Elevated expression of various cytokines has been reported in ischemic injury of the kidney (Goes et al. 1995; Takada et al. 1997; Lemay et al. 2000). Renal ischemia-reperfusion injury has also been documented to augment leukocyte accumulation in the outer renal medulla (Thadhani et al. 1996) and cytokine release from activated leukocytes (Camussi et al. 1998). Other causes of ARF include various toxins (e.g. radiocontrast agents and certain antibiotics) and rhabdomyolysis. Rhabdomyolysis results in ARF for several reasons. Swelling of the muscles leads to hypovolemia and decreased renal perfusion. Myoglobin, leaking out of the damaged muscle cells, is also directly toxic to tubular cells (Holt et al. 2001).

The diagnosis of ARF in clinical practice in the ICU is most often based on indirect measures of GFR, plasma urea and creatinine concentrations, and infrequently also on the clearance of creatinine over a 24-hour urine collection. Recently, a novel marker of renal function, cystatin C, was proposed to be more sensitive than plasma creatinine for various forms of chronic renal dysfunction (Newman et al. 1995; Plebani et al. 1998; Randers et al. 2000; Woitas et al. 2000). Cystatin C is produced by all nucleated cells (Barrett et al. 1984; Abrahamson et al. 1990), is eliminated solely by glomerular filtration (Tenstad et al. 1996), is freely filtered in the glomerulus, is neither secreted nor reabsorbed by renal tubules, and is metabolized by proximal tubular cells so that it does not return to blood flow in an intact form (Jacobsson et al. 1995). The

effectiveness of cystatin C in predicting ARF (Delanaye et al. 2004; Herget-Rosenthal et al. 2004, 2005; Villa et al. 2005) and as a risk factor for mortality (Jernberg et al. 2004; Shlipak et al. 2006) has been studied little.

Hospital and ICU mortality rates of patients with ARF have varied from 37%, to 88% (Groeneveld et al. 1991; Brivet et al. 1996; Schwilk et al. 1997). Due to comorbidities, mortality and morbidity rates may remain high after the initial recovery. However, few studies exist on mortality after one month or after hospital discharge; on the long term mortality (Gopal et al. 1997; Korkeila et al. 2000; Morgera et al. 2002; Maynard et al. 2003), or on attainable quality of life after ARF (Gopal et al. 1997; Morgera et al. 2002; Maynard et al. 2003). The health-related quality of life (HRQoL) after intensive care has been shown to vary according to the diagnostic category of the patients (Diaz-Prieto et al. 1998; Badia et al. 2001; Granja et al. 2002). This has led to an increasing demand for studies concerning HRQoL in different critically ill patient populations (Angus et al. 2003).

This clinical study investigates the value of different markers and scoring methods in predicting mortality of ARF patients. Furthermore, these patients' outcomes, as HRQoL and long-term survival, and the effect of intermittent hemodiafiltration (HDF) on myoglobin elimination from plasma in severe rhabdomyolysis are evaluated.

2. REVIEW OF THE LITERATURE

2.1. Definition of acute renal failure

Generally, ARF is defined as an abrupt and sustained decline in renal function, which results in disturbances in electrolyte and acid-base homeostasis, derangement in extracellular fluid volume, and retention of nitrogenous waste products (Nissenson 1998). In the absence of specific markers for kidney dysfunction, this general definition has been applied in over 30 different ways in the literature thus far (Table 1). The degree of renal dysfunction required for a diagnosis of ARF has varied from a modest increase in serum or plasma creatinine concentration to severe renal dysfunction and the need for RRT. Although some definitions have been complex, the ones most commonly used have relied on the easily measurable and unique functions of the kidney, namely urine output and excretion of nitrogenous waste products. The clearance of nitrogenous waste products has usually been estimated indirectly by measuring serum or plasma creatinine concentration or plasma urea concentration. As reviewed by Thadhani et al. (1996), the most popular definitions of ARF are an increase in plasma creatinine of 0.5 mg/dL (44 μmol/L) (Solomon et al. 1994) or of more than 50% over the baseline value, a reduction in the creatinine clearance of 50%, and a decrease in renal function that results in a need for RRT. When urine output is included in the definition, the requirement of daily urine output has commonly been less than 400-500mL or 0.5mL/kg/h.

The need for a universally accepted definition of ARF has recently led to a proposal for a consensus definition by the Acute Dialysis Quality Initiative (ADQI) workgroup (Bellomo et al. 2004). The workgroup proposed that the most useful definition of ARF is a rapid and sustained decrease in GFR or urine output, or both. They also suggested that an ideal definition should consider change from baseline and include both acute and chronic renal disease. The resulting definition, the RIFLE definition, classifies ARF into five severity categories (risk, injury, failure, loss of renal function, and end-stage renal disease) (Table 2). However, its validation process in large prospective studies is still incomplete (Bouman 2003), as is the recommended statistical development of the classification (Ruttimann 1994).

Table 1. *Definitions of acute renal failure (ARF) used in published studies.*

Reference	Definition
Hou et al. 1983	Rise in SCr ≥44 µmol/L (0.5 mg/dL) if baseline SCr ≤168 µmol/L (1.9 mg/dL) or ≥88 µmol/L (1.0 mg/dL) if baseline SCr 177-433 µmol/L (2.0-4.9mg/dL) or ≥133 µmol/L (1.5 mg/dL) if baseline SCr ≥442 µmol/L (5.0 mg/dL)
Solomon et al. 1994	Rise in SCr ≥44 µmol/L (0.5 mg/dL) within 48 h
Brivet et al. 1996	SCr >310 µmol/L (3.5 mg/dL) or BUN >36mmol/L (100 mg/dL) or ↑SCr/BUN >100% in chronic renal insufficiency
Chertow et al. 1996	Rise in SCr ≥88 µmol/L (1.0 mg/dL) in 24-48 h
Kapoor et al. 1996	Rise in SCr ≥25%
Levy et al. 1996	Rise in SCr ≥25% to at least 177 µmol/L (2.0 mg/dL) in two days
Liano et al. 1996	Rise in SCr >177 µmol/L [≥50% if prior mild renal dysfunction (SCr ≤264 µmol/l)] or elevated SCr on admission
Shilliday et al. 1997	SCr >180 µmol/L
Mangano et al. 1998	Failure: need for RRT, dysfunction: SCr >177 µmol/L with an SCr increase >62 µmol/L
Vivino et al. 1998	SCr >177 µmol/L (2 mg/dL) or an increase of over 20% from the baseline
Behrend et al. 1999	Rise in SCr ≥80 µmol/L (0.9 mg/dL) to at least 177 µmol/L (2.0 mg/dL) (if baseline SCr <177 µmol/L) or rise in SCr ≥133 µmol/L (1.5 mg/dL) (if baseline SCr ≥177 µmol/L)
Conlon et al. 1999	SCr >88 µmol/L (1.0 mg/dL) postoperatively
Hirschberg et al. 1999	SCr ≥265 µmol/L (3.0 mg/dL) with baseline SCr <159 µmol/L (1.8 mg/dL) or acute decrease in CrCl to ≤25 mL/min
Fiaccadori et al. 2000	Rise in PCr >50% in 24-48 h or increase from baseline >1 mg/dL with known renal insufficiency
Sirivella et al. 2000	Urine output <30 mL/h for 2-3 h and ↑SCr >44 µmol/L (0.5 mg/dL) or >50% or ↓estimated CrCl >50%
Wang et al. 2000	Rise in SCr ≥44 µmol/L (0.5 mg/dL) or 25% within 48 h
Bates et al. 2001	ARF: rise in SCr ≥50% to at least 177 µmol/L (2.0 mg/dL), SARF: rise in SCr ≥100% to ≥265 µmol/L (3.0 mg/dL)
Bellomo et al. 2001	ARI: SCr >120 µmol/L or rise >60 µmol/L and plasma urea >8 mmol/L or rise >4 mmol/L or diuresis <800 mL/24 h or <200 mL/6h, ARFS: SCr >240 µmol/L or rise >120 µmol/L and plasma urea >16 mmol/L or rise >8 mmol/L or diuresis <400 mL/24 h or <100 mL/6h, SARFS: ARI or ARFS requiring RRT
John et al. 2001	SCr >265 µmol/L (3.0 mg/dL) and/or urine output<10 mL/h
Mehta et al. 2001	SCr >177 µmol/L (2 mg/dL) or blood urea nitrogen ≥14.3 mmol/L (40 mg/dL) / rise in SCr ≥88.4 µmol/L (1.0 mg/dL)
Metnitz et al. 2002	Need for RRT
Mehta et al. 2004	↑SCr ≥44 µmol/L (0.5 mg/dL) if baseline SCr ≤133 µmol/L (1.5 mg/dL) or ↑SCr ≥88 µmol/L (1.0 mg/dL) if baseline SCr ≥133 µmol/L (1.5 mg/dL)
Uchino et al. 2004	RRT and/or diuresis <200 mL/12 h or P-urea >30 mmol/L or BUN >31 mmol/L (86 mg/dL) or S-K >6.5 mmol/L
Bagshaw et al. 2005	Need for RRT <48 h after ICU admission and SCr >150 µmol/L
Fernandez et al. 2005	SCr >221µmol/L (2.5 mg/dL)
Morelli et al. 2005	SCr >150 µmol/L
Uehlinger et al. 2005	SCr >350 µmol/L or urine output <20mL/h

SCr=serum creatinine concentration, PCr=plasma creatinine concentration,CrCl=creatinine clearance, BUN=blood urea nitrogen, P-urea=plasma urea,S-K=serum potassium, ARI=acute renal injury, ARFS=acute renal failure syndrome, SARFS=severe ARFS, RRT=renal replacement therapy.

Table 2. *The RIFLE definition of acute renal failure. Adapted from Bellomo et al.(2004).*

	GFR criteria	or	Urine output criteria
Risk	Increased serum creatinine x 1.5 or decreased GFR >25%		<0.5 mL/kg/h x 6 h
Injury	Increased serum creatinine x 2 or decreased GFR >50%		<0.5 mL/kg/h x 12 h
Failure	Increased serum creatinine x 3 or decreased GFR >75% or acute rise in serum creatinine ≥44 μmol/L to more than 350 μmol/L		<0.3 mL/kg/h x 24 h or anuria x 12 h
Loss	Persistent ARF, complete loss of kidney function >4 weeks		
ESRD	End-Stage Renal Disease (>3 months)		

GFR= glomerular filtration rate, ARF= acute renal failure.

2.2. Incidence of acute renal failure

Acute renal failure (ARF) is a significant medical problem. The overall incidence has varied from 8 (Korkeila et al. 2000) to 11 per 100 000 inhabitants/year (Bagshaw et al. 2005) (80-110 per million inhabitants/year) to 209 per million inhabitants over nine months (279 per million inhabitants/ year) (Liano et al. 1996). The incidence is comparable with the incidence of acute respiratory distress syndrome (ARDS), which has been reported as 114-198 patients per million inhabitants/year (Arroliga et al. 2002). It is, however, significantly less than that reported for severe sepsis: 3000 per million inhabitants/ year (Angus et al. 2001). ARF develops in about 5 % of all hospitalized patients (Hou et al. 1985) and in 5-25% of patients admitted to ICUs (Groeneveld et al. 1991; Brivet et al. 1996; de Mendonca et al. 2000; Metnitz et al. 2002; Uchino et al. 2005). The highest incidence, approximately 50%, has been reported in patients with septic shock (Rangel-Frausto et al. 1995).

2.3. Etiology of acute renal failure

Table 3. *Etiology of acute renal failure.*

	Etiology	Reference (reviews)
Prerenal causes	**Reduced kidney perfusion**	Hou et al. 1983
	Volume depletion	Hou et al. 1983
	Hypotension	Hou et al. 1983
	Low cardiac output	Hou et al. 1983
	Renal arterial vasoconstriction	Hou et al. 1983
	Drugs	
	NSAIDs	Markowitz et al. 2005
	ACE inhibitors	Verme-Gibboney 1997
	Cyclosporin A	Olyaei et al. 1999
Postrenal causes	**Obstruction of urinary outflow**	Thadhani et al. 1996
Intrinsic renal causes	**Acute tubular necrosis**	Lameire et al. 2005
	Prolonged renal ischemia	Reineck et al. 1980 (not review)
	Sepsis	Harris et al. 1991
	Myoglobin (rhabdomyolysis)	Slater et al. 1998
	Other nephrotoxins (radiocontrast medium, aminoglycosides, vancomycin, fluoroquinolones, amikacin, amphotericin B, aciclovir)	Harris et al. 1991
	Interstitial nephritis	
	Autoimmune diseases	Thadhani et al. 1996
	Bacterial and viral infections	Thadhani et al. 1996
	Drugs (penicillins, cephalosporins, azithromycin, NSAIDs)	Cooper et al. 1987
	Glomerular nephritis	Jennette et al. 1990
	Various mechanisms (cisplatin, metothrexate, cyclosporine A, gold)	Cooper et al. 1987

NSAIDs= nonsteroidal anti-inflammatory drugs, ACE= angiotensin-converting enzyme.

Prerenal causes

Prerenal causes include all clinical conditions, that result in reduced perfusion in the kidneys (Hou et al. 1983); that comprise volume depletion, hypotension, low cardiac output, renal arterial vasoconstriction, and obstruction of renal arteries. The reduction in GFR in prerenal ARF is thus at least partly physiologic. Drugs that can induce prerenal ARF include nonsteroidal anti-inflammatory agents (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors. NSAIDs, which inhibit prostaglandin synthesis, reduce GFR by blocking the effect of locally released vasodilatory prostaglandins in hypo-perfusion states, as reviewed by Markowitz et al. (2005). ACE inhibitors may induce prerenal ARF by decreasing the production of angiotensin II, which is needed in preserving glomerular capillary hydrostatic pressure by constriction of glomerular efferent arterioles (for review, see Verme-Gibboney 1997). Cyclosporin A is also known to cause vasoconstriction of both afferent and efferent arterioles, leading to a decrease in renal perfusion and thus also to a decrease in GFR (Olyaei et al. 1999).

Postrenal causes

Postrenal ARF occurs when urinary outflow is obstructed, increasing the pressure in Bowman's capsules and reducing the hydrostatic pressure needed for glomerular filtration to take place. Renal vasoconstriction subsequently occurs and GFR falls (Yucha et al. 1997). A requirement for the development of ARF is that the obstruction of urine outflow is below bladder level or the patient has only one kidney, as a second kidney can easily compensate for the loss of the first (Thadhani et al. 1996).

Intrinsic renal causes

Renal causes for ARF include all pathological processes in the kidney. The most common form of renal ARF is acute tubular necrosis (ATN), which is also the predominant form of ARF seen in septic patients (Harris et al. 1991). ATN can be classified as either intrinsic renal (Lameire et al. 2005) or prerenal (Lameire et al. 2003) since the boundary between prerenal ARF and ATN is fuzzy. Prolonged renal ischemia leads to increased renal damage and prerenal ARF develops into ATN (Reineck et al. 1980). ATN can also be caused by various nephrotoxins (Harris et al. 1991), such as radiocontrast agents and several antibacterial, -fungal, or -viral therapies, including aminoglycosides, vancomycin, fluoroquinolones, amikacin, ampho-tericin B, and aciclovir. In addition, ATN is frequently caused by the toxic effects of myoglobin in rhabdomyolysis (Slater et al. 1998).

Other intrinsic renal causes of ARF are more infrequent. Drugs that produce ARF by an intrinsic renal mechanism other than ATN usually do so by causing interstitial nephritis (Cooper et al. 1987). Such drugs include sulfonamide antibiotics, penicillins, cephalosporins, azithromycin, and NSAIDs. Cisplatin, metothrexate, cyclosporine A, and gold are all also known to trigger ARF by various mechanisms. Interstitial nephritis can also be precipitated by a wide range of autoimmune diseases and bacterial- or viral infections (Thadhani et al. 1996).

Rapidly progressive glomerular nephritis, which is a source of ARF developing outside the hospital, is often caused by underlying vasculitis (Jennette et al. 1990).

In patients with pre-existing chronic renal dysfunction, the etiology of ARF is an insult to the kidney that is superimposed on the kidney dysfunction already present. This results in more severe ARF (Bouman et al. 2003) and is usually defined as "acute on chronic" renal failure (Bellomo et al. 2001; Bouman et al. 2003). Table 3 summarizes the etiology of ARF.

Risk factors

Surprisingly few studies have focused on the risk factors for developing ARF. A large multinational study reported the most important risk factors present on hospital admission to be age over 65 years, infection, history of chronic heart failure, lymphoma, leukemia, or liver cirrhosis (de Mendonca et al. 2000). Older age and liver cirrhosis were also found to predict development of ARF in a study with 257 septic/SIRS patients (Yegenaga et al. 2004). Another study of 240 ARF patients found previous heart disease, stroke, pulmonary disease, diabetes mellitus, cancer, connective tissue disease, chronic renal dysfunction, and alcoholism to be predictive of ARF (Bagshaw et al. 2005). Large epidemiologic studies support the role of older age, diabetes mellitus, underlying chronic renal disease, and heart failure as risk factors for developing ARF (Parfrey et al. 1989; Mangano et al. 1998; Nash et al. 2002; Schmekal et al. 2004). Several studies on cardiac surgery patients have identified preoperative renal dysfunction and emergency operation/ heart failure during operation to be major risk factors for developing ARF postoperatively (Conlon et al. 1999; Stallwood et al. 2004; Wijeysundera et al. 2006). One of these, a large study of 10 751 patients, reported the other risk factors for developing severe ARF and the need for RRT to be diabetes mellitus, previous cardiac surgery, and low left ventricular ejection fraction (Wijeysundera et al. 2006). Other risk factors for ARF in cardiac surgery have been reported to be the use of perfusion and perfusion time, age, arteriovascular disease, obesity, male gender, mitral valve operation, need for a contrapulsator, and diabetes mellitus (Bove et al. 2004; Stallwood et al. 2004). In trauma patients, age, hemoperitoneum, hypotension and shock, rhabdomyolysis, need for mechanical ventilation, severity of trauma, and Glasgow Coma Score of less than 10 have been described as risk factors for ARF (Vivino et al. 1998). In severe inflammation, such as in sepsis or SIRS, there is an abundance of inflammatory mediators in the circulation. This is a predisposing factor for ARF since inflammatory mediators play a role in the pathogenesis of ARF, as reviewed by Wan et al. (2003). The etiology of ARF is often multifactorial. ARF develops as a consequence of several simultaneous insults to the kidney such as septic inflammation and hypotension or the use of nephrotoxic agents. Table 4 shows common risk factors for ARF.

Table 4. *Risk factors for acute renal failure (ARF).1= risk factor, 0= not a risk factor.*

Reference	Total (n)	ARF (n)	Age	Liver disease	Dia-betes	Cardiac dys-function	Hypo-tension	Chronic renal disease	Ventilatory dysfunction
de Mendonca et al. 2000	1411	348	1	1		1	1		1
Yegenaga et al. 2004	257	28	1	1	0		1		0
Bagshaw et al. 2005	240	240		0	1	1		1	1
Mangano et al. 1998	2222	171	1		1	1		1	
Schmekal et al. 2004	232	232				1		1	
Conlon et al. 1999	2672	211	1		1	1			
Stallwood et al. 2004	2199	53	1		1			1	
Bove et al. 2004	5068	171	1		1	1		1	
Vivino et al. 1998	153	48	1				1		1
Total	14454	1502	7	2	5	6	3	5	3

2.4. Pathogenesis of acute tubular necrosis

In critically ill patients, ARF is often multifactorial and almost always ATN has a central role in the pathogenesis. In fact, in the literature, the terms “ARF” and “acute tubular necrosis” are frequently used interchangeably. Therefore, this section focuses on the pathogenesis of acute tubular necrosis, which in itself is extremely complex. Although factors related to the pathogenesis of acute tubular necrosis have been studied in detail, controversy exists regarding the basic mechanisms of the pathogenesis. The pathogenesis apparently depends on the cause of acute tubular necrosis. Studies concerning the pathogenesis therefore often concentrate on one of the underlying causes: ischemia, sepsis, SIRS, or nephrotoxic agents.

Ischemic acute tubular necrosis

Ischemic acute tubular necrosis is basically a result from a mismatch between oxygen delivery and demand in the kidney. Ischemic injury to the kidney leads to adenosine triphosphate (ATP) depletion in renal tubular cells, impairing many cellular processes and inducing loss of cell polarity (Lieberthal et al. 1998). Mislocalization of the ionic pumps also occurs, most importantly, the relocation of N-K ATPase to the apical membrane (Molitoris et al. 1992). The net result is cell necrosis, as reviewed by Thadhani et al.(1996). Several studies have provided evidence that in acute tubular necrosis a large part of cell death also occurs by apoptosis (Shimizu et al. 1993; Jaffe et al. 1997; Oberbauer et al. 1999; Ortiz et al. 2000).

After the initial ischemic event, during reperfusion, a second insult to the kidney occurs. Studies have shown leukocyte accumulation in the outer renal medulla during reperfusion (Linas et al. 1988; Willinger et al. 1992). Both neutrophils and mononuclear cells infiltrate the kidneys, but which ones are more important in ischemia-reperfusion injury is still being debated (Linas et al. 1988; Klausner et al. 1989; Rabb et al. 2000; Burne et al. 2001). Leukocyte adhesion is a central event in leukocyte recruitment to injured tissue, and the renal endothelium seems to play a major role in this. Following ischemic injury, the endothelial cells begin to produce proinflammatory cytokines and adhesive molecules (Adler et al. 1999). Leukocyte activation leads to generation of free radicals and cytokines (Camussi et al. 1998). Supporting evidence exists from several studies that report increased expressions of various cytokines in ischemic injury in animals (Goes et al. 1995; Takada et al. 1997; Lemay et al. 2000) and increased IL-6 levels in renal injury (Smith et al. 2000). Inflammatory response is further augmented by upregulation of leukocyte-activating chemokines by inflammatory cytokines (Rahman et al. 1998; Donnahoo et al. 1999). Oxygen free radicals have also been shown to be capable of activating T-cells (Chaudhri et al. 1986). IL-10, on the other hand, has been documented to ameliorate injury in posttransplant ischemic ARF (Deng et al. 2001). Supporting evidence comes from studies where eliminating IL-10 has exacerbated ischemic kidney injury (Hess et al. 1997).

Sepsis-induced acute tubular necrosis

The pathogenesis of ATN in sepsis has been investigated little. The evidence of pathogenesis of ARF in sepsis in these studies has also been inconsistent. Some evidence points to ischemia of the kidney being the leading cause. Some studies report a reduction in total renal blood flow during endotoxemia (Badr et al. 1986; Kikeri et al. 1986). Others, however, have found global and medullary renal blood flow during hyperdynamic sepsis to be normal or increased (Ravikant et al. 1977; Di Giantomasso et al. 2003). Whether the major underlying cause of ARF in sepsis is local vasoconstriction and ischemia or the inflammatory response is under debate (Wan et al. 2003; Lameire 2005). The contribution of proinflammatory response is favored by a study where tumor necrosis factor (TNF) receptor

knock-out mice were resistant to endotoxin-induced ARF (Cunningham et al. 2002). Another study found that neutralization of TNF results in a smaller decrease in GFR during endotoxemia in mice (Knotek et al. 2001). However, a study of rabbits with endotoxemic shock reported no protection from kidney injury with neutralization of TNF by monoclonal antibodies (Rodriguez-Wilhelmi et al. 2003). Finally, apoptosis has been shown to be one mechanism of endotoxin- and cytokine-induced tubular cell death in ARF (Jo et al. 2002).

Nephrotoxic acute tubular necrosis

1. Rhabdomyolysis-induced acute tubular necrosis

Rhabdomyolysis, the breakdown of skeletal muscle, can be caused by various factors, with direct muscle trauma, energy depletion, and genetic defect of muscle-cell metabolism being among the most common. However, all causes seem to lead to rhabdomyolysis via a common pathway: the release of calcium from the sarcolemma and cytocolic calcium overload (Knochel 1993), leading to muscle cell damage and the release of myocyte constituents into the circulation. One of the key compounds released is myoglobin, a heme-containing protein that plays a major role in development of rhabdomyolysis-induced ARF (Slater et al. 1998).

While the precise mechanism by which myoglobin induces ARF is still unclear, three mechanisms have been proposed: heme protein-induced oxidant injury by lipid peroxidation to renal tubular cells, renal vasoconstriction, and cast formation in the renal tubuli (Holt et al. 2001). The presence of oxidative stress in the pathogenesis of ARF is supported by an experimental model of myoglobinuric ARF in which treatment with antioxidants reduced morphological changes in renal cells (Chander et al. 2003) The lipid peroxidation has been suggested to occur either by release of free ferrous (Fe^{2+}) iron, resulting in generation of hydroxyl radicals via the Fenton reaction, or by redox cycling of ferric (Fe^{3+}) myoglobin to lipid peroxidation, inducing ferryl ($[Fe=O]^{2+}$) myoglobin (Hogg et al. 1994) Renal vasoconstriction is said to result from the formation of potent renal vaso-constrictors, F_2-isoprostanes, as a by-product of lipid peroxidation (Morrow et al. 1990; Takahashi et al. 1992; Moore et al. 1998), or from heme-protein induced nitric oxide (NO) scavenging (Sharma et al. 1987; Neto et al. 1988; Furchgott et al. 1991; Gorbunov et al. 1995), which inhibits NO-induced vasodilatation. Cast formation in the renal tubuli occurs when the heme protein concentration in renal tubuli increases in rhabdomyolysis. Cast formation is further increased when urine pH decreases, as the heme protein aggregates with Tamm-Horsfall proteins in renal tubular cells, as reviewed by Zager (1996). In addition, cast formation increases the concentration of myoglobin in renal tubuli. Finally, hypovolemia-induced reduction in renal blood flow has a central role in the pathogenesis of rhabdomyolysis-induced acute tubular necrosis. Following muscle injury, a marked decrease can occur in blood volume, as fluid is taken up into the damaged muscle cell (Slater et al. 1998).

2. CONTRAST MEDIA-INDUCED ACUTE TUBULAR NECROSIS

The pathogenesis of contrast media-induced acute tubular necrosis is in many ways similar to the pathogenesis of rhabdomyolysis-induced acute tubular necrosis. Evidence has emerged for a direct toxic effect of contrast media on renal tubular cells (Battenfeld et al. 1991; Ueda et al. 1993; Katholi et al. 1998; Hizoh et al. 2002). Furthermore, contrast media induce ARF nonspecifically by hyperosmolality, which has been found to augment renal vasoconstriction (Reed et al. 1983) and thus ischemia to the kidney. In addition, GFR is reduced by an increase in intratubular hydrostatic pressure created by the high osmolarity of urine (Katzberg 1997). A meta-analysis of randomized trials revealed that the risk for nephropathy was lower with hypo-osmolar than with hyperosmolar contrast media (Barrett et al. 1993). Risk seemed to be highest when hyperosmolar contrast media was used in patients with pre-existing renal disease. Finally, several studies have demonstrated an association between a high dose of contrast medium and greater risk for ARF (McCullough et al. 1997; Freeman et al. 2002; Rihal et al. 2002).

2.5. Diagnosis of acute renal failure

Diagnostic markers

1. INULIN CLEARANCE - GOLD STANDARD

In renal failure, inulin clearance is regarded as the gold standard, i.e. most accurate diagnostic technique available, for determining GFR (Perrone 1992). Drawbacks with the inulin clearance method are that it requires an intravenous infusion, is laborious, and is expensive.

2. ISOTOPE AND IOHEXOL CLEARANCES

Plasma clearances of various isotopes (^{51}Cr-EDTA, ^{99m}Tc-DTPA, ^{125}I-iothalamate) (Dubovsky et al. 1982; Perrone et al. 1990) and iohexol (Brown et al. 1991) have also performed well as markers of renal function. Only minimal differences have been observed between inulin clearance and isotope (Rehling et al. 1984; Perrone et al. 1990) or iohexol (Brown et al. 1991) clearance. These methods are, however, too complicated for clinical use.

3. SERUM / PLASMA CREATININE AND CREATININE CLEARANCE

Creatinine measurement from serum or plasma is the most commonly used marker of renal function. Serum and plasma concentrations of creatinine have been shown to correspond to each other (Mazzachi 2000). Creatinine is an endogenous marker generated in muscle from creatine and creatine phosphate (Wyss et al. 2000). Creatinine fulfills a central requirement for an endogenous marker of GFR; it is freely filtered in the glomerulus. However, it is also secreted in the tubulus in substantial amounts. The tubular secretion is proportional to the plasma creatinine concentration, leading to an overestimation of GFR. A decrease of at least 50% in GFR is usually needed for serum/plasma creatinine concentration to increase markedly (Renkin et al. 1974). The accuracy of serum/plasma creatinine determination is also influenced by its generation being

proportional to muscle mass (Perrone et al. 1992). Finally, age, gender, and diet have been shown to affect serum/plasma creatinine concentration (Jacobsen et al. 1980; James et al. 1984).

Creatinine clearance typically provides an estimation of the 24-hour excretion of creatinine in urine. However, it overestimates GFR due to tubular secretion of creatinine, and many studies have found high day-to-day variation (Paterson 1967; Guillausseau et al. 1988). Furthermore, a review on the subject concluded that creatinine clearance-based estimates of GFR show a worse correlation with actual GFR than estimates based on plasma creatinine (Walser 1998).

4. Plasma urea /blood urea nitrogen

Urea nitrogen is an end-product of protein metabolism in the liver. It is freely filtered in the glomerulus. However, it undergoes renal tubular reabsorption and is therefore unreliable as an estimate of GFR. Moreover, the production rate of urea nitrogen is not stable; it depends on liver function, protein intake, and catabolism (Reynolds 1992; Waterlow 1994). Catabolism-inducing drugs, such as corticosteroids, increase plasma urea/blood urea nitrogen concentrations via increased protein degradation (Wray et al. 2002). Plasma urea/blood urea nitrogen concentration has also been shown to increase in patients with gastrointestinal bleeding (Stellato et al. 1980). This is thought to result from the degradation of blood in the gastrointestinal tract and is more profound in upper gastrointestinal hemorrhage (Snook et al. 1986; Ernst et al. 1999).

5. Serum cystatin C

Cystatin C, a member of the cystatin superfamily, is an inhibitor of cysteine proteases (Barrett et al. 1984). It is a novel marker of renal function, and, theoretically, is an ideal endogenous marker of renal function. It meets all requirements for such a marker; it is produced at a constant rate by all nucleated cells (Barrett et al. 1984; Abrahamson et al. 1990), eliminated solely by glomerular filtration (Tenstad et al. 1996), freely filtered in the glomerulus due to its low molecular weight, and is neither secreted nor reabsorbed by renal tubules. Cystatin C is metabolized by proximal tubular cells so that it does not return to blood flow in an intact form (Jacobsson et al. 1995).

A few limitations for the use of cystatin C in clinical practice exist. It has previously been described as being independent of gender (Finney et al. 2000; Johnston et al. 2004) and muscle mass (Vinge et al. 1999). However, one study reported that increasing body mass index and cigarette smoking were associated with a higher serum cystatin C concentration (Galteau et al. 2001). These results were supported by another study, in which increasing age, weight, increasing height, and C-reactive protein (CRP) as well as male gender, and smoking were all independently associated with higher serum cystatin C levels (Knight et al. 2004). In the latter study, the results could not be solely explained by the variables' effects on renal function, as the results were adjusted for GFR. The reference range

for cystatin C is stable through most of adulthood, but after the age of 50 years cystatin C concentration tends to increase with decreasing GFR (Finney et al. 2000; Randers et al. 2000; Johnston et al. 2004). In children older than one year, cystatin C has been shown to be independent of age (Bokenkamp et al. 1998; Finney et al. 2000). Large doses of glucocorticoids have been described to increase serum cystatin C concentration (Bjarnadottir et al. 1995; Risch et al. 2001). Also, thyroid function affects serum cystatin C concentrations (Fricker et al. 1944; den Hollander et al. 2003; Wiesli et al. 2003). Moderate removal of cystatin C from plasma during hemodialysis has been demonstrated, but the precise amount remains obscure (Thysell et al. 1988; Kabanda et al. 1994; Tian et al. 1997; Campo et al. 2004).

Based on evidence from several studies, cystatin C seems to be a superior marker for detection of early renal dysfunction in chronic renal impairment (Plebani et al. 1998; Randers et al. 1998, 2000; Woitas et al. 2000; Mussap et al. 2002; Christensson et al. 2004; Grubb et al. 2005). It has particularly been evaluated in subject groups such as children (Willems et al. 2003; Grubb et al. 2005), the elderly (Van Den Noortgate et al. 2002), and patients with decreased muscle mass (Thomassen et al. 2002), where estimating GFR by creatinine-based methods is known to yield unreliable results. A meta-analysis of 20 studies concluded that cystatin C appears to be a more accurate marker than creatinine (Laterza et al. 2002). However, several studies have provided contradictory evidence, finding cystatin C to not be superior to other estimates of GFR (Risch et al. 2001; Van Den Noortgate et al. 2002; Willems et al. 2003; Gabutti et al. 2004). Studies on cystatin C in ARF and in critical illness are sparse. One recent study in critically ill patients reported cystatin C to increase faster than creatinine in ARF patients (Herget-Rosenthal et al. 2004). The study also reported thyroid function and use of glucocorticoids to not have an effect on cystatin C concentration. Another study found cystatin C to have a high correlation with creatinine clearance in critically ill patients (Villa et al. 2005). Good predictive ability concerning small decreases in GFR in critically ill patients has been noted in two studies (Delanaye et al. 2004; Villa et al. 2005). Another study reported a more rapid increase in serum cystatin C than in serum creatinine after nephrectomy (Herget-Rosenthal et al. 2005). A small study on 29 septic patients observed no correlation between cystatin C and the occurrence of ARF (Mazul-Sunko et al. 2004).

Research of cystatin C in outcome prediction is sparse. A recent study reported serum cystatin C concentration to independently predict long-term mortality in hospitalized patients with acute coronary syndrome (Jernberg et al. 2004). These authors also reported the relative risk for death to increase with increasing serum cystatin C concentration. Another study found increasing serum cystatin C concentration to be associated with increasing mortality in a cohort of well-functioning elderly persons (Shlipak et al. 2006). Finally, one small study on critically ill patients treated with RRT noted higher serum cystatin C concentrations in nonsurvivors than in survivors (Balik et al. 2005).

Models for estimation of glomerular filtration rate

Several formulas for the estimation of GFR exist (Cockcroft et al. 1976; Schwartz et al. 1987; Levey et al. 1999). Two of these, the Cockcroft-Gault formula (Cockcroft et al. 1976) and the "Modification of Diet in Renal Disease" (MDRD) formula (Levey et al. 1999), are typically used in adults. The older Cockcroft-Gault formula is used more extensively. For men, GFR (mL/min/1.73m^2) can be calculated as follows:

$$\frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine (mg/dL)}}$$

For women, the equation needs to be multiplied by 0.85. The MDRD formula can be calculated as follows:

GFR (mL/min/1.73m^2) = exp(5.228 - 1.154 x ln(SCr (mg/dL)) - 0.203 x ln(age) - (0.299 if female) + (0.192 if African-American)).

For both formulas, conversion of serum creatinine concentrations from µmol/L to mg/dL has to be made by dividing the values by 88.4. The MDRD formula formula takes into account the effects of age, gender, and race and has recently been recommended by the ADQI workgroup (Bellomo et al. 2004). In the original study by Levey et al. (1999) the MDRD formula performed better as an estimate of GFR than the Cockcroft-Gault formula. The debate of whether the Cockcroft-Gault formula or the MDRD formula gives more accurate estimations of GFR continues today (Vervoort et al. 2002; Pierrat et al. 2003; Rigalleau et al. 2005; Poggio et al. 2006).

Severity scoring

1. General severity-of-illness scoring methods

The Acute Physiology and Chronic Health Evaluation (APACHE) II score is a measure of the general severity of illness, originally developed for calculating risk for death in critically ill patients (Knaus et al. 1985). The score is determined using the patient's age, premorbid chronic health, and twelve physiologic variables representing current severity of illness. Sequential Organ Failure Assessment (SOFA) is aimed at determining the severity of organ dysfunctions (Vincent et al. 1996). Subscores for six organ systems are determined, and the score is calculated by addition of these subscores. SOFA score originally was not created for outcome prediction, but it has performed well (de Mendonca et al. 2000; Janssens et al. 2000; Mehta et al. 2002; Peres Bota et al. 2002; Carbonell et al. 2004).

2. ARF-specific severity- of-illness scoring methods

ARF-specific severity-of-illness scoring methods can be divided into two groups; those that focus on determining the severity of ARF (Vincent et al. 1996; Bellomo et al. 2001; Bellomo et al. 2004) and those that determine the general severity of illness in ARF patients (Liano et al. 1993; Paganini et al. 1996; Chertow et al. 1998; Lins et al. 2000; Mehta et al. 2002). The number of scoring methods of the first group is limited. The SOFA

score can be classified in the first group, as it includes a specific subscore for renal dysfunction. The SOFA subscore for renal organ dysfunction is determined by plasma creatinine concentration and urine output as follows: score 0: plasma creatinine 110 µmol/L (nonARF), score 1: plasma creatinine 110-170 µmol/L, score 2: plasma creatinine 171-299 µmol/L, score 3: plasma creatinine 300-440 µmol/L or urine output 201-500 mL/ 24 h, and score 4: plasma creatinine >440 µmol/L or urine output <200 mL/ 24 h (Vincent et al. 1996). Besides the renal SOFA score, only two other ARF-specific scoring methods that focus on determining the severity of renal dysfunction exist: the RIFLE classification (Bellomo et al. 2004) (Table 2) and the Bellomo classification (Bellomo et al. 2001) (Table 1). These scoring methods deal with ARF as a continuum and distinguish mild, moderate, and severe forms from one another. They also contain specific criteria for "acute on chronic" renal failure.

The second group of ARF-specific scoring grades the general severity of illness in ARF patients. The main focus is on prediction of survival. The scores calculate a probability or odds ratio for death using mainly the patient's age and gender and the presence of other organ failures (Liano et al. 1993; Paganini et al. 1996; Chertow et al. 1998; Lins et al. 2000; Mehta et al. 2002).

2.6. Prevention and treatment of acute renal failure

Several therapeutic approaches have been suggested for prevention of ARF. However, only a few of them have been verified as valid. The cornerstones for prevention of ARF include elimination of nephrotoxic medication (Lameire et al. 2003), hydration with saline (Solomon et al. 1994; Shimazu et al. 1997), and maintenance of adequate perfusion pressure (Bellomo et al. 2005). In many cases, decreasing the dosage of a nephrotoxic agent helps. The risk for ARF has been shown to decrease with a once-daily dose versus multiple doses of aminoglycosides (Prins et al. 1993). In addition, lowering the dose of radiocontrast agents decreases mortality (McCullough et al. 1997).

Hydration

Saline hydration has been proven effective in reducing the risk of radiocontrast-induced nephropathy (McCullough et al. 1997; Taylor et al. 1998; Stevens et al. 1999; Mueller et al. 2002; Merten et al. 2004). In patients at risk for contrast-media nephropathy, no benefit over hydration with saline alone has been found with mannitol, dopamine, or furosemide (Solomon et al. 1994; Stevens et al. 1999). In rhabdomyolysis, aggressive fluid therapy decreases the risk of ARF (Shimazu et al. 1997; Gunal et al. 2004). Whether crystalloids or colloids are ideal resuscitation fluids in critical illness is under debate (Schierhout et al. 1998; Choi et al. 1999; Waikar et al. 2000). Some evidence has emerged suggesting that hydroxyethyl starch (HES) has side-effects on renal function. It promotes osmotic nephrosis presenting as proximal tubular swelling and vacuolization (Legendre et al. 1993). One study compared the effects of HES with gelatin infusions in brain-dead donors and found the incidence of ARF after transplantation to be significantly

higher in the HES group than in the gelatin group (Cittanova et al. 1996). HES and gelatine were also compared in a multicenter trial in patients with severe sepsis, where administration of HES was revealed to be an independent risk factor for ARF (Schortgen et al. 2001). Hence, gelatine is generally recommended over HES in patients at risk for developing ARF.

Diuretics

Loop diuretics have been used widely to promote diuresis in oliguric ARF. However, several studies have provided evidence of their lack of effectiveness in preventing ARF (Lassnigg et al. 2000; Uchino et al. 2004). Some studies have suggested that use of loop diuretics is associated with increased mortality in ARF patients (Mehta et al. 2002), but a large multicenter study did not confirm these findings (Uchino et al. 2004). A recent meta-analysis also could not demonstrate increased mortality with the use of furosemide in ARF, nor did it, however, find furosemide useful in ARF (Ho et al. 2006).

Urine alkalization

Urine alkalization with sodium bicarbonate infusion is commonly used in rhabdomyolysis to prevent ARF. To what extent urine alkalization affects myoglobin clearance and metabolic rate remains unclear since controversy exists regarding the metabolism of myoglobin. However, in acidic surroundings, metmyoglobin has been shown to induce vasoconstriction (Heyman et al. 1997), and hemoglobin accumulation in the kidney increased in an animal model (Zager et al. 1989). It has also been suggested that the alkalization of diuresis prevents ARF by reducing the redox cycling of the ferric - ferryl myoglobin (Moore et al. 1998), thus preventing lipid peroxidation, the death of renal tubular cells, and renal vasoconstriction. However, some studies have demonstrated that GFR has little effect on myoglobin clearance rate in rhabdomyolysis, suggesting that myoglobin metabolism is mainly extrarenal (Wakabayashi et al. 1994; Lappalainen et al. 2002).

N-acetylcysteine

N-acetylcysteine (NAC) in the prevention of ARF has been investigated with controversial results. Some studies have yielded positive results in prevention of radiocontrast-induced ARF (Tepel et al. 2000; Kay et al. 2003), whereas others have found it to possess no beneficial effects (Briguori et al. 2002). One study found NAC to reduce the occurrence of ARF after contrast media, but did not find any benefits in long-term outcome (Miner et al. 2004). Moreover, a study on the effect of NAC in preventing of ARF after coronary artery bypass graft surgery yielded negative results (Burns et al. 2005). The mechanism by which NAC prevents ARF is suggested to be suppression of oxidant stress (Drager et al. 2004). Some evidence exists that NAC might reduce serum creatinine concentration by extrarenal mechanisms, and the decrease seen in serum creatinine concentration might therefore not reflect an actual increase in GFR (Hoffmann et al. 2004). However, the side-effects of oral NAC are minimal, and most meta-analyses

recommend its use in patients with chronic renal dysfunction (Birck et al. 2003; Isenbarger et al. 2003; Alonso et al. 2004; Liu et al. 2005). A recent systematic review, including 15 studies and 1776 patients, reported a decrease in serum creatinine concentrations after NAC, but did not find any clinically significant benefits in prediction of ARF (Pannu et al. 2004). These authors also reported significant heterogeneity between trial results. Finally, two recent meta-analyses found the heterogeneity of clinical studies to be too great for any definitive conclusions (Kshirsagar et al. 2004; Zagler et al. 2006). Kshirsagar et al. (2004) conducted a meta-analysis with 16 prospective clinical trials and 1538 patients and noted that the heterogeneity of current clinical studies prevents any meaningful conclusions being drawn. The meta-analysis by Zagler et al. (2006) included 13 trials and 1892 patients with chronic renal insufficiency undergoing coronary angiography. In that meta-analysis, the risk reduction for ARF was 0.68, but the upper limit of the 95% CI for the risk reduction exceeded 1.0 in the NAC group. Evidence exists that the effect of NAC on serum creatinine concentration might result for reasons other than improving GFR (Genet et al. 2000; Hoffmann et al. 2004). Therefore, the effect of NAC on firm clinical end-points, such as occurrence of ARF or mortality, is difficult to interpret from serum creatinine concentration results.

Vasodilatory agents

1. DOPAMINE

Traditionally, low-dose dopamine infusion has been the method of choice for renal protection. Several studies have been published on prevention of ARF and on treatment of early ARF. The majority of these studies have not provided evidence for renal protective effects of low-dose dopamine (Gare et al. 1682; Chertow et al. 1996; Palsson et al. 1997; Bellomo et al. 2000). The results were confirmed by a systematic review (Marik 2002) and two meta-analyses. In the meta-analysis by Kellum et al. (2001), dopamine did not prevent mortality, onset of acute renal failure, or need for dialysis. Another meta-analysis by Friedrich et al. (2005) with 61 trials and 3359 patients found no effect of low-dose dopamine on mortality, need for RRT, or adverse events. Low-dose dopamine therapy has been associated with such side-effects as impaired hemodynamics (Leier et al. 1978; Stephan et al. 1990; Chiolero et al. 1991; Duke et al. 1994), impaired gastrointestinal motility (Tarling et al. 1997; Dive et al. 2000), increased gut ischemia despite an increase in splanchnic perfusion (Giraud et al. 1984; Segal et al. 1992; Marik et al. 1994), impaired pituitary gland function (Van den Berghe et al. 1994), and suppression of respiratory drive (Welsh et al. 1978; Nishino et al. 1981; Olson et al. 1982; Ward et al. 1983; Shoemaker et al. 1989; van de Borne et al. 1998). A wide consensus therefore exists regarding the ineffectiveness of low-dose dopamine in renal protection.

2. FENOLDOPAM

Fenoldopam is a selective dopamine α-1 agonist (Singer et al. 1998), that decreases renal vascular resistance and increases renal blood flow and GFR (Bakris et al. 1999). Animal studies have shown that fenoldopam affects renal hemodynamics and may improve renal perfusion (Bakris et al. 1999). Similar results have been demonstrated in nonrandomized clinical studies (Madyoon et al. 2001). However, in randomized placebo-controlled double-blind trials, those results could not be verified (Stone et al. 2003; Bove et al. 2005). A recent study on ICU patients found fenoldopam ineffective in reducing mortality or the need for RRT (Tumlin et al. 2005). Another study of 315 patients with chronic renal dysfunction who received radiocontrast agents revealed no benefit on mortality (Stone et al. 2003).

3. ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic peptide (ANP) is secreted by cardiac atria. In animal studies, it has been shown to promote preglomerular arteriolar dilatation and postglomerular arteriolar constriction (Shaw et al. 1987). One human study reported improved GFR and reduced need for RRT, but no effect on mortality (Rahman et al. 1994). Several studies about ANP have failed to show improved survival of ARF patients (Kurnik et al. 1998; Meyer et al. 1999). On the other hand, an 11% (95% CI 1-21%) decrease in dialysis-free survival has been reported with ANP in a placebo-controlled multicenter study of 378 critically ill patients with nonoliguric ARF (Allgren et al. 1997). In this study, worsening outcome was thought to be due to systemic hypotension induced by ANP. The authors also reported an 18% (95% CI 5-32%) improved dialysis-free survival in oliguric ARF patients, but these findings could not be verified in another study (Lewis et al. 2000).

Other agents

Several studies have shown that hydration with mannitol does not prevent ARF (Gubern et al. 1988; Ip-Yam et al. 1994; Solomon et al. 1994; Stevens et al. 1999). Mannitol increases oxygen consumption in the renal outer medulla, and it has been proposed to actually be harmful in ARF (Solomon et al. 1994). A recent study in trauma patients with rhabdomyolysis found no decrease in the need for RRT or mortality in patients who had received mannitol with sodium bicarbonate versus in those who had not (Brown et al. 2004). Controversial results also exist. Administering mannitol, furosemide, and dopamine simultaneously has been reported to decrease the need for RRT markedly in postoperative ARF patients with adequate cardiac output (Sirivella et al. 2000).

Theophylline and aminophylline, competitive adenosine antagonists, have been proposed to reduce the radiocontrast agent-induced ARF. A recent meta-analysis by Ix et al. (2004) with seven randomized controlled trials and 480 patients, found the increase in serum creatinine concentration after contrast medium to be 11.5 μmol/L less in patients who had received either theophylline or aminophylline than in patients who had not (Ix et al. 2004). However, they concluded that the clinical

significance of this small difference is unclear.

Calcium channel blockers have been suggested to prevent reperfusion injury and be beneficial in preventing ATN. Randomized studies on calcium channel blockers in post-transplant ATN were recently systematically analyzed by Shilliday et al. (2005). They found calcium channel blockers to reduce the incidence of postoperative ATN if administered during the kidney transplant operation. However, they observed no significant difference in mortality and concluded that the number of standardized studies on this subject is too small for definitive conclusions.

Other substances that have been investigated are numerous. They include growth factors (Hirschberg et al. 1999; Hladunewich et al. 2003; Nagano et al. 2004), ascorbic acid (Norio et al. 2003; Klouche et al. 2004), magnesium (Wong et al. 1989; Dowd et al. 1995; Bäcklund et al. 2000), and allopurinol (Alatas et al. 1996; Kim et al. 1999; Willgoss et al. 2003).

Renal replacement therapy

Common indications for acute RRT include volume overload, hyperpotassemia, metabolic acidosis, and uremia (Lameire et al. 2005). In critically ill adults, the dialysis modality chosen is usually either intermittent or continuous venovenous RRT. The effect of dialysis modality on mortality in critically ill patients has been investigated widely. No clear difference in mortality between patients treated with intermittent or continuous modalities has been found (John et al. 2001; Mehta et al. 2001; Augustine et al. 2004; Uehlinger et al. 2005). One of the studies reported a higher mortality rate for continuous renal replacement therapy (CRRT) than for intermittent therapy. However, after adjusting for severity of illness, no differences were present between the groups (Mehta et al. 2001). A meta-analysis with a total of 1400 patients found no mortality difference between continuous and intermittent RRT with a relative risk of 0.93 (95% CI 0.79-1.09) (Kellum et al. 2002). However, they also reported great heterogeneity between studies. After adjusting for severity of illness and study quality, a decrease in mortality was observed for the CRRT group (Kellum et al. 2002). A more recent large multicenter trial also could not demonstrate a difference in 60-day mortality in multiorgan dysfunction patients treated with intermittent hemodialysis versus continuous veno-venous hemodiafiltration (Vinsonneau et al. 2006). However, evidence suggesting more favorable effects on hemodynamics with CCRT has been provided (John et al. 2001). In addition, early administration and a bigger dose of RRT have been proposed to reduce mortality. Random assignment of patients into groups receiving different doses of continuous venovenous hemofiltration (CVVH) demonstrated improved survival in patients in the higher-dose group (Ronco et al. 2000). Similar results were reported in a study with intermittent hemodialysis where patients were assigned to receive daily or alternate-day treatments (Schiffl et al. 2002).

2.7. Outcome of acute renal failure

Mortality

The mortality rate in ARF varies. Mortality rates in ICU have ranged between 43% and 63% (Groeneveld et al. 1991; de Mendonca et al. 2000) and for the hospital mortality overall between 58% and 74% (Brivet et al. 1996; Neveu et al. 1996; Uchino et al. 2005). The great variation in mortality rates reflects the correlation between the degree of renal dysfunction required for the definition of ARF and the corresponding mortality (Kellum et al. 2002). A recent review evaluating 80 clinical studies on ARF concluded that the short-term mortality rate is around 50% (Ympa et al. 2005). Also, a large multi-national, multicenter study with 29 269 critically ill patients reported a hospital mortality rate of 60% among ARF patients (Uchino et al. 2005).

Comorbidities affect mortality and morbidity, which remain high after initial recovery (Gopal et al. 1997; Korkeila et al. 2000; Morgera et al. 2002; Maynard et al. 2003). Substantial long-term sequelae after critical illness have been described (Niskanen et al. 1996; Hurel et al. 1997; Ridley et al. 1997; Kaarlola et al. 2003). A recent study on cardiopulmonary bypass patients requiring RRT for ARF postoperatively found their long-term outcome to be relatively good: 1- and 5-year survival rates were 53% and 52%, respectively (Luckraz et al. 2005). Moreover, only 2% of patients required long-term renal support. Similar results were reported in a study on ARF patients treated with RRT (Bell et al. 2005), with the overall 60-day mortality rate being 55%, after which mortality decreased rapidly; the overall 6-month mortality rate was 60%.

Quality of life

Quality of life has been evaluated by measuring patients' health-related quality of life (HRQoL), which covers three main aspects; the patient's physical, psychological, and social status (Guyatt et al. 1993; Angus et al. 2003; Wu et al. 2004). In heterogeneous ICU patient populations, the most decreased dimension of HRQoL varies. Some studies describe the worst results in the 'physical' dimension (Tian et al. 1995), and others in the 'emotional' (Granja et al. 2002; Kaarlola et al. 2003) or 'usual activities' (Konopad et al. 1995; Metnitz et al. 2002) dimension. A study comparing the HRQoL of former ICU patients with a community sample found that the former ICU patients reported worse HRQoL in 6 of the 8 scales (Flaatten et al. 2001). As diagnosis has been shown to affect HRQoL after intensive care (Hurel et al. 1997; Ridley et al. 1997; Diaz-Prieto et al. 1998; Badia et al. 2001; Granja et al. 2002), an increasing demand for studies on HRQoL in different critically ill patient populations has arisen (Angus et al. 2003). Studies on HRQoL after ARF are sparse (Gopal et al. 1997; Korkeila et al. 2000; Morgera et al. 2002), as recently reviewed by Radhakrishnan et al. (2006). However, one study confirmed by a simplified version of the Nottingham Health Profile that 69% of patients discharged from hospital were satisfied with their current health (Gopal et al. 1997). Limitations in the physical

domain was the most common complaint in 42% of the patients taking part in the evaluation of HRQoL (Gopal et al. 1997). Supporting evidence comes from another study, where loss of energy and limitations in physical mobility were the predominant complaints according to the Nottingham Health Profile six months after ARF (Korkeila et al. 2000). Another study reported that 77% of questionnaire respondents assessed their current health status as good or excellent (Morgera et al. 2002).

The long-term effects of critical illness and intensive care on HRQoL observed in ARF patients are comparable with those seen in other critically ill patients. A study on heterogeneous ICU patients reported reduced general health and physical functioning, and increased pain six years after intensive care (Kaarlola et al. 2003). A study of 79 mechanically ventilated patients reported HRQoL, as measured by the Nottingham Health Profile, to be significantly reduced compared with the normal population (Combes et al. 2003). In acute respiratory distress syndrome patients, several studies have documented decreased long-term HRQoL (Davidson et al. 1999; Schelling et al. 2000; Herridge et al. 2003; Orme et al. 2003). One year after intensive care, the HRQoL of patients with severe peritonitis remains lower than that of the general population, as measured by Short Form 36 (SF 36) (Scheingraber et al. 2002).

Prognostic factors

ARF has been found to be an independent predictor of mortality (Levy et al. 1996; de Mendonca et al. 2000; Metnitz et al. 2002). Calculated likelihood ratios for the risk of death in ARF patients are 1.96 (95% CI 1.66-2.32), 2.80 (95% CI 2.36-3.31), and 7.74 (95% CI 6.77-8.85), respectively. Hospital mortality in ARF patients has been documented to be significantly higher than in nonARF ICU patients, 63% vs. 16%, (Metnitz et al. 2002). The calculated difference in mortality in this study was 47% (95% CI 44-51%). Moreover, ICU mortality in ARF patients has been reported to be three times as high as in other ICU patients, 43% vs. 14% (de Mendonca et al. 2000). The calculated difference in mortality was 29% (95% CI 23-34%). In the same study, the calculated odds ratio for death was 1.59 (95% CI 1.23-2.06) for oliguric ARF. However, an odds ratio for death as high as 5.5 has also been reported in contrast media-induced ARF (Levy et al. 1996) and as high as 6.6 in amphotericin B-induced ARF (Bates et al. 2001). Multiple organ dysfunction and other comorbidities contribute to the high mortality rate associated with ARF (Biesenbach et al. 1992). Independent predictors of ICU and hospital mortality have been described in numerous studies (Table 5). The most common factors directly related to ARF mortality are age, mechanical ventilation, other organ failures, and “late” occurrence of ARF. Renal recovery is usually good. It has been reported to be 78% (95% CI 68-85%) at one year (Bagshaw et al. 2005). In critical illness, age and preadmission quality of life have been documented to be the main factors affecting HRQoL after ICU discharge (Vazquez Mata et al. 1992; Wehler et al. 2001). One of the studies also showed that organ failures increased the risk for deteriorated physical health, but did not affect mental

health, six months after hospital discharge (Wehler et al. 2001). The HRQoL was measured in this study using a scale validated by Fernandez et al. (1996).

In these studies, the risk for death was expressed as odds ratios (ORs) and/or risk ratios (RRs) (Table 5). ORs compare the mortality rate with the survival rate in ARF vs. nonARF patients. ORs can be calculated as follows:

$$\frac{\text{Deceased ARF patients/Surviving ARF patients}}{\text{Deceased nonARF patients/Surviving nonARF patients}}$$

RR represents the risk of death in patients with ARF compared with the risk in nonARF patients, and can be calculated as follows:

$$\frac{\text{Deceased ARF patients/All ARF patients}}{\text{Deceased nonARF patients/All nonARF patients}}$$

However, in evidence-based medicine, the use of likelihood ratios (LRs) has been recommended over ORs or RRs in prognostic studies (Okada 2005). The advantage of LRs is that they can be combined with the pretest probability of death to calculate a total likelihood of death after the test. Positive likelihood ratios (LR+) represent the likelihood of death in ARF patients/the likelihood of death in nonARF patients, and can be calculated as sensitivity/1-specificity or as:

$$\frac{\text{Deceased ARF patients/All deceased patients}}{1 - (\text{Surviving nonARF patients/All surviving patients})}$$

In evidence based medicine calculating likelihood ratios retrospectively for studies, which have not reported them, is usually recommended. However, the majority of the studies included in Table 4 did not report the exact number of patients in all their categories. Hence, LRs could not be retrospectively calculated, and ORs are reported in Table 5.

Several scoring systems have been developed to predict mortality in ARF (Liano et al. 1993; Paganini et al. 1996; Chertow et al. 1998; Lins et al. 2000, 2004; Bellomo et al. 2001, 2004; Mehta et al. 2004) (Table 6). In all but two of these, hospital mortality is used in the prediction model. However, the classification by Chertow et al. uses 30-day mortality in the prediction model and that by Paganini et al. fails to mention which mortality is used in the prediction model. The RIFLE classification (Bellomo et al. 2004) is presented in Table 2. All of these scoring methods performed well when they were validated in single-center studies for outcome prediction in ARF patients. However, when the same scoring methods were tested in a large multinational study, the predictive abilities of several turned out to be lower than those originally published (Uchino et al. 2005). The RIFLE classification has been evaluated by two studies, which have shown that the RIFLE stage Failure presents much higher mortality than the stages Risk or Injury (Abosaif et al. 2005; Bell et al. 2005). Abosaif et al. found the difference in mortality between patients in stage Failure vs. other patients to be 27% (95% CI 12-42%). In the study by Bell et al., mortality was 58% in stage Failure vs. 24% in stage Risk and 22% in stage

Injury. The Bellomo score (Bellomo et al. 2001) has been documented to correlate with mortality, but not to be an independent predictor for it (Ostermann et al. 2005). Ostermann et al. reported the ORs for death according to the Bellomo classification to be 0.18 (no ARF), 2.12 (ARI), 4.8 (ARFS), 8.37 (SARFS), and 2.4 (end-stage renal failure). The ability of general severity-of-illness scoring methods to predict outcome in ARF is unclear. Some studies have reported good ability for APACHE II score and the SOFA score (van Bommel et al. 1995; Parker et al. 1998; Fiaccadori et al. 2000; Chen et al. 2001; Peres Bota et al. 2002), whereas others have provided contradictory data (Halstenberg et al. 1997; Fiaccadori et al. 2000; Carbonell et al. 2004; Abosaif et al. 2005; Lima et al. 2005).

Most of the scores mentioned above were developed according to the recommendations for predictive tools (Laupacis et al. 1994; Ruttimann 1994), where the patient sample is a well-defined cohort, univariate analysis is used to determine variables associated with mortality, the model's discriminative power is determined by receiver operating characteristic (ROC) analysis, and the model is validated using multivariate analysis. However, two of the scores, RIFLE and Bellomo, are based on consensus and have not yet been validated.

Several biomarkers, used in the diagnosis of ARF or in determining the pathogenesis of ARF, have also been tested for their ability to predict outcome in ARF (Simmons et al. 2004). The most commonly studied biomarkers are plasma/serum creatinine concentration, plasma urea concentration, and blood urea nitrogen (Paganini et al. 1996; Mehta et al. 2002; Lima et al. 2005).

Table 5. *Major independent factors directly related to mortality in acute renal failure (ARF). OR=odds ratio, RR=risk ratio, RRT=renal replacement therapy, ICU=intensive care unit, APACHE II=Acute Physiology and Chronic Health Evaluation II.*

Reference	Independent predictors of mortality
Groeneveld et al. 1991	Age, cardiovascular failure, pulmonary failure, RRT
Brivet et al. 1996	Age, previous health status, hospitalization before ICU admission, late ARF, sepsis, oliguria, APACHE II score, number of failing organs
Liano et al. 1996	Coma, assisted respiration, hypotension, jaundice, oliguria
Paganini et al. 1996	Male gender, respiratory failure requiring mechanical ventilation, hematological dysfunction, bilirubin >2.0 mg/dL, absence of surgery, serum creatinine on first RRT day, increasing number of failing organs, increased blood urea nitrogen on admission
Schwilk et al. 1997	Cardiovascular (OR 7.7)/ hepatic (OR 6.3)/ respiratory (OR 3.6)/ neurological failure (OR 3.0), massive transfusion (OR 5.3), age over 60 years (OR 3.7)
Chertow et al. 1998	Male gender (OR 3.70), oliguria (OR 4.39), mechanical ventilation (OR 2.95), acute myocardial infarction (OR 5.90), acute stroke or seizure (OR 7.35), chronic immunosuppression, hyperbilirubinemia, metabolic acidosis (OR 0.93)
Behrend et al. 1999	Oliguria, mechanical ventilation, decreased cardiac function
Mehta et al. 2002	Age (OR 1.02), male gender (OR 2.36), respiratory (OR 2,62)/ liver (OR 3.06)/ hematological failure (OR 3.40), serum creatinine level (OR 0.71), blood urea nitrogen (OR 1.02), log urine output (OR 0.64), heart rate (OR 1.01)
Hoste et al. 2003	Age, need for vasoactive therapy/ mechanical ventilation/ RRT
Lins et al. 2004	Age, albumin, prothrombin time, respiratory support, heart failure, sepsis, bilirubin, hypotension
Schroeder et al. 2004	Underlying disease, length of stay in ICU, use of catecholamines, late ARF, correlation of APACHE II score and ICU length of stay
Bagshaw et al. 2005	Comorbidities, liver disease, APACHE II score, septic shock, RRT
Lima et al. 2005	Age ≥65 years, blood urea nitrogen ≥70 mg/dL, septic origin of ARF, previous hypertension
Ostermann et al. 2005	Nonsurgical admission, emergency surgery, late ARF, mechanical ventilation, number of organ failures
Uchino et al. 2005	Use of vasopressors (OR 1.95), mechanical ventilation (OR 2.11), septic (OR 1.36) or cardiogenic shock (OR 1.41), hepatorenal syndrome (OR 1.87)

Table 6. *Calculation of five ARF- specific scores for prediction of hospital /30-day mortality.*

Reference	Score	Validation	Max. score
Liano et al. 1993	(0.032 x age in decades) – (0.086 for male gender) – (0.109 for nephrotoxic origin) + (0.109 for oliguria) + (0.116 for hypotension) + (0.122 for jaundice) + (0.150 for coma) – (0.154 for consciousness) + (0.182 for assisted respiration) + 0.210	Logistic regression	if >0.9 mortality 100%
Paganini et al. 1996	(2 points for male gender) + (3 points for mechanical ventilation) + (3 points for hematological dysfunction) + (3 points for bilirubin >2.0 mg/dL) + (1 point for absence of surgery) + (0 points if no other organ failures/2 points for 2-3 other organ failures/3 points for 3-7 other organ failures) + (1 point for 0-50 mg/dL rise in blood urea nitrogen/2 points for >50 mg/dL rise in blood urea nitrogen) + (3 points if SCr ≤2.0 mg/dL/1 point if SCr 2.0-5.0 mg/dL/ 0 points if SCr >5.0 mg/dL on the day of RRT start)	Logistic regression	20
Chertow et al. 1998	(0.6991 for male gender) + (0.8128 for oliguria) + (0.0557 x total bilirubin [mg/dL]) + (0.6215 for mechanical ventilation) + (1.1245 for stroke or seizure) + (1.1432 for acute myocardial infarction) + (0.8643 for chronic immunosuppression) – (0.0555 x bicarbonate) – (0.3139 x albumin [g/dL])	ROC, proportional hazards regression	18
Lins et al. 2000	$SHARF_0$: (7 x age in decades) + (6 x albumin category) + (3 x prothrombin time category) + (39 for respiratory support) + (9 for heart failure) + 52, $SHARF_{48}$: (7 x age in decades) + (6 x albumin category) + (3 x prothrombin time category) + (43 for respiratory support at 48 h) + (16 for heart failure at 48 h)	ROC, linear regression	0h: 236, 48h: 247
Bellomo et al. 2001	ARI: (PCr >1.6 mg/dL/ rise ≥0.8 mg/dL) and (P-urea >22 mg/dL/ rise >11 mg/dL and/or urine output <800 mL/24 h/<200 mL/6h), ARFS: (PCr >3.1 mg/dL /rise ≥1.6 mg/dL) and (P-urea >45 mg/dL/ rise >22 mg/dL and/or urine output <400 mL/24 h/ <100 mL/6h), SARFS: ARI/ ARFS + RRT	Not validated	
Lins et al. 2004	SHARF II_0: (3.0 x age in decades) + (2.6 x albumin category) + (1.3 x prothrombin time category) + (16.8 for respiratory support) + (3.9 for heart failure) + (2.8 x bilirubin in mg/dL) + (27 for sepsis) + (21 for hypotension) -17, SHARF II_{48}: (3.9 x age in decades) + (3.3 x albumin category) + (1.7 x prothrombin time category) + (23.7 for respiratory support at 48 h) + (8.8 for heart failure at 48 h) + (2.5x bilirubin in mg/dL) + (24 for sepsis) + (17 for hypotension) -28	ROC, linear regression	Not mentioned
Mehta et al. 2004	(0.0170x age) + (0.8605 for male gender) + (0.0144 x blood urea nitrogen) – (0.3398 x creatinine) + (1.2242 for hematological failure) + (1.1183 for liver failure) + (0.9637 for respiratory failure) + (0.0119 x heart rate) – (0.4432 x log[urine output]) – 0.7207	ROC, logistic regression	Not mentioned

SCr=serum creatinine concentration, RRT=renal replacement therapy, SHARF=Stuivenberg Hospital Acute Renal Failure scoring system, ARI=acute renal injury, ARFS=acute renal failure syndrome, SARFS=severe ARFS, P-urea=plasma urea concentration, ROC=receiver operating characteristic, Max. score=maximum score.

3. AIMS OF THE STUDY

The general aim was to evaluate the outcome of critically ill patients with ARF and factors related to outcome. Predictive tools in the development of ARF and the mortality of ARF patients were investigated. Specific objectives were as follows:

1. To evaluate two newly proposed definitions of ARF in assessing the severity of illness (I).

2. To determine the evolution of laboratory markers and pro- and anti-inflammatory cytokines in ARF (II-III), specifically:

   a) to determine the evolution of monocyte HLA-DR expression (II), and plasma concentrations of interleukins 6, 8, and 10 in critically ill SIRS patients with ARF (II),

   b) to determine the evolution of serum cystatin C in critically ill patients with ARF (III), and to compare the diagnostic accuracy of serum cystatin C with plasma creatinine in development of ARF (III).

3. To evaluate possibilities of affecting the development of ARF by studying the effect of intermittent hemodiafiltration on myoglobin elimination from plasma in severe rhabdomyolysis (IV).

4. To assess the outcome of critically ill patients with ARF (I-III, V), in terms of short-term (I-III, V) and long-term mortality (V) and HRQoL (V).

5. To evaluate prediction of outcome in critically ill patients with ARF (I-III): by two ARF-specific severity scores (I), by monocyte HLA-DR expression and plasma concentrations of interleukins 6, 8, and 10 (II), and by serum cystatin C concentration (III).

4. SUBJECTS AND METHODS

4.1. Patients

Inclusion criteria and formation of the study population

Altogether 1662 patients were included in the study. The number of treatment episodes was 1691, with 29 patients having two separate episodes. The flowchart of Studies I-V is presented in Figure 1. Twenty-seven of the patients were included in two studies. Twenty-six patients were first included in Study II and then in Study V. One patient was first included in Study III and then in Study V. However, the study designs and endpoints differed from each other. Studies II and III were prospective, assessing predictive factors for outcome, and the Study V was retrospective, evaluating the HRQoL after ARF. Characteristics of the study population are shown in Table 7.

Study I comprised 668 consecutive adult patients admitted to two ICUs within 11 months in 2005. During this time 26 patients had two separate treatment periods, the earlier one of which was included in the primary analysis. The secondary analysis included all 694 consecutive treatment episodes. Nine dialysis-dependent patients with chronic end-stage renal failure and two patients receiving RRT for nonrenal reasons were excluded. The final study population consisted of 658 patients with 683 treatment episodes.

Study II included a total of 103 consecutive adult ICU patients admitted in 1998-1999 with systemic inflammatory response syndrome (SIRS). SIRS was defined according to the consensus criteria presented by Bone et al (1992): temperature >38ºC or <36ºC; heart rate >90 beats /min; respiratory rate ≥20 breaths /min or PaCO2 <4.3 kPa; white blood cell count $>12x10^9$ cell/L or $<4x10^9$ or >10% immature forms. SIRS was verified by the presence of two or more of the criteria.

Study III consisted of a total of 199 consecutive adult ICU patients admitted during a period of nine months in 2003. Three patients had two separate treatment episodes and were included twice in the study, resulting in the total number of treatment episodes of 202. The separate treatment episodes were handled as separate patients, as the episodes were clearly distinct temporally. One of those episodes ended up in the ARF group and five in the nonARF group. Table 8 provides details of the patients in Study III.

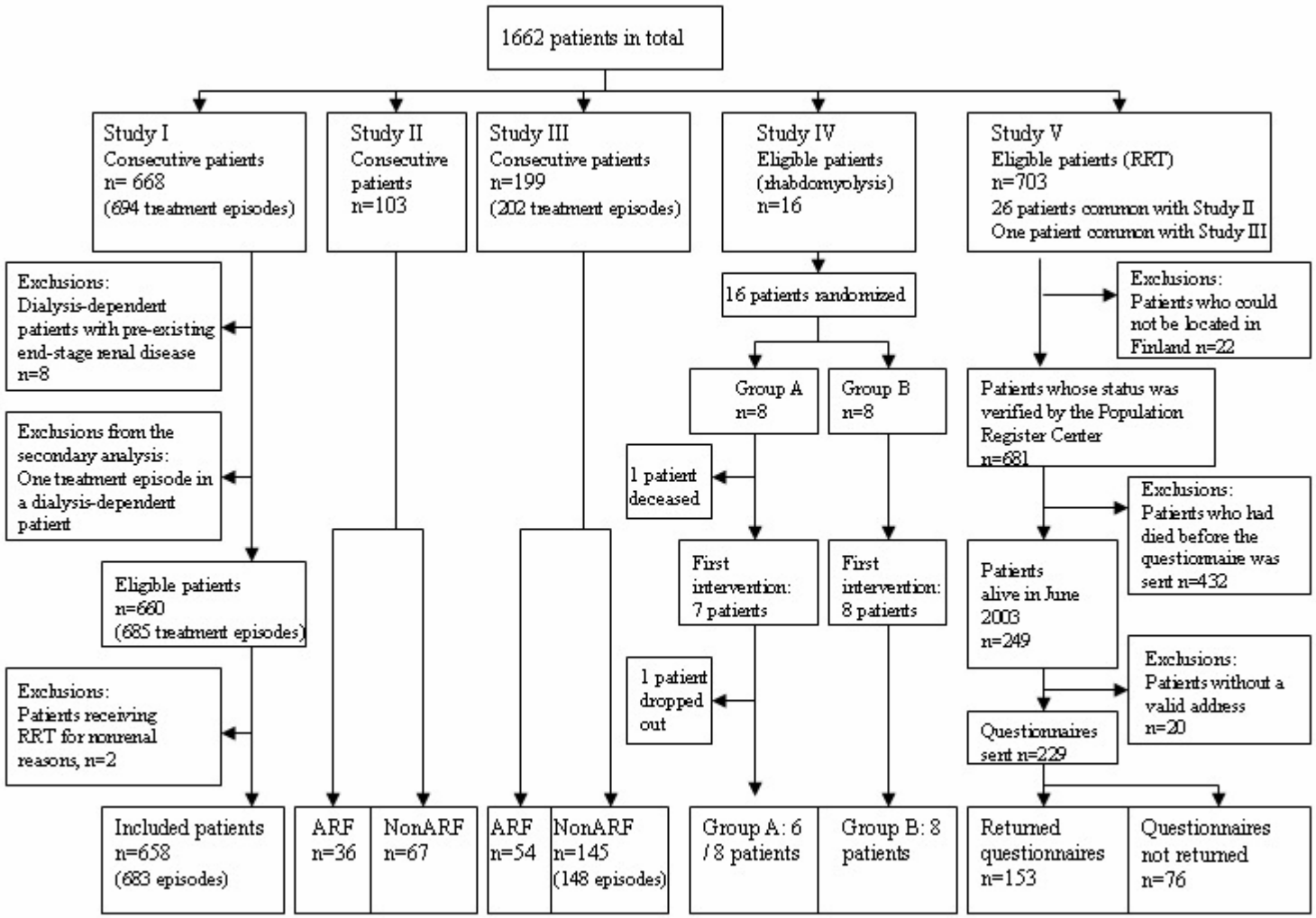


Figure 1. *Flowchart of the study population*

Table 7. *Demographics of the study population.*

	Study I (n=658)		Study II (n=103)		Study III (n=202)		Study VI	Study V
	ARF (n=74)	**NonARF (n=584)**	**ARF (n=36)**	**NonARF (n=67)**	**ARF (n=54)**	**NonARF (n=148)**	**(n=16)**	**(n=681)**
Age (years)	55 (47-67)*	64 (55-74)*	55 (47-62)	51 (42-60)	57 (51-66)	54 (44-64)	62 (53-69)	61 (49-71)
Gender (M/F)	47 / 27	383 / 201	29 / 7	46 / 21	43 / 11*	94 / 54*	10 / 6	477 / 204
Treated in ICU	74 (100%)	584 (100%)	36 (100%)	67 (100%)	54 (100%)	148 (100%)	16 (100%)	534 (78%)
APACHE II	22 (18-27)*	14 (11-18)*	16 (12-20)*	9 (7-14)*	18 (16- 24)*	13 (9-18)*	13 (11-18)	18 (14-21)
SOFA								
admission	11 (9-14)*	6 (4-8)*	10 (8-12)*	6 (4-9)*	12 (9-13)*	7 (5-9)*		
maximum	12 (10-14)*	7 (5-9)*						
RRT							4 (2-9)	9 (7-12)
Length of stay								
ICU (days)	7 (3-12)*	4 (2-6)*			11 (6-19)*	5 (3-9)*		
hospital (days)	15 (7-29)*	11 (7-16)*	17 (8–45)	18 (11-33)			15 (11-27)	

*Values are presented as median (interquartile range) or number (%). ARF= acute renal failure. RIFLE= Risk, Injury, Failure, Loss of renal function, End-stage renal disease, ICU=intensive care unit, APACHE II= Acute Physiology and Chronic Health Evaluation II, SOFA= Sequential Organ Failure Assessment. *p<0.05*

Table 8. *Indications for intensive care in patients with and without acute renal failure (ARF) in Study III.*

Indication for intensive care	ARF patients (n=54)	NonARF patients (n=148)	p
Sepsis	19 (35.2%)	21 (14.2%)	0.001
Other infection	11 (20.4%)	36 (24.3)	NS
Other noninfectious state	24 (44.4%)	91 (61.5%)	0.03

Values are presented as number of patients (percentage) and compared by X^2-test. NS = not significant

Study IV included 16 adult emergency patients with rhabdomyolysis treated in an acute renal replacement unit between July 2002 and November 2005. Inclusion criteria were the presence of rhabdomyolysis and plasma myoglobin concentration over 10 000 µg/L at the time of allocation. All eligible patients were recruited, and none refused to participate. However, one patient died less than one hour after the first intervention commenced and another patient was lost after the first intervention because some of the laboratory samples were lost. These patients were considered deviations from the protocol.

Study V comprised 703 patients receiving RRT for ARF during 1998-2002 at Helsinki University Central Hospital. Indications for RRT were presence of ARF defined as an acute increase in serum creatinine to at least 500 µmol/L or plasma urea over 35 mmol/L (38%) or a sudden rise in serum creatinine over 50 µmol/L and oliguria /anuria /severe metabolic acidosis /hyperpotassemia (59%) or rhabdo-myolysis with oliguria and no response to forced alkaline diuresis (3%). Twenty-two patients were excluded because the Population Register Centre could not verify their status (dead or alive). Hence, 681 patients ultimately participated. In Study V, two patients were included twice as they had separate treatment episodes far apart from each other.

Definitions for acute renal failure

In Study I, ARF was defined according to two methods for defining and scoring the severity of illness in ARF: the RIFLE classification (Bellomo et al. 2004) and the Bellomo classification (Bellomo et al. 2001). The RIFLE classification defines five stages (Table 2), and the Bellomo classification three stages of ARF (Table 1). Patients treated with RRT for renal indications were considered to have ARF (stage "Failure"/ stage "severe acute renal failure syndrome") regardless of their serum creatinine concentration or urine output. The RIFLE classification does not include precise criteria for RRT patients. On the other hand, the classification also does not clearly state that RRT should be ignored. The interpretation of the RIFLE criteria in Study I was based on one of the documents in the Acute Dialysis Quality Initiative website concerning ARF research and the definition of ARF. This states that all patients needing acute RRT for renal reasons should be considered as having acute renal failure (www.ccm.upmc.edu/adqi/adqi02.html, 1. Defining acute renal failure, Work Group Report) (Bouman C et al. 2003). The RIFLE definition was also used in Study III, where patients were classified as having ARF if they fulfilled the RIFLE criteria for stage "Failure". In Study II, patients were considered to have ARF if they met the SOFA score criterion (2 points or more) for ARF: serum creatinine levels higher than 170 µmol/L (2.0 mg/dL) (Vincent et al. 1996). None of the patients had a known history of chronic renal failure, nor had they ever received any form of RRT, and hence, no criteria for "acute on chronic" ARF were needed. In Study IV, the incidence of ARF was not recorded since all patients received prophylactic RRT as part of the protocol. In Study V ARF,

was defined as the need for acute RRT for renal reasons.

4.2. Methods

Study design

Study I. A prospective cohort of 668 consecutive patients treated in two ICUs of a tertiary care hospital was investigated. The prevalence of ARF was calculated and classified according to the RIFLE (Bellomo et al. 2004) and the Bellomo (Bellomo et al. 2001) classifications. In patients with a history of plasma creatinine level above the upper range limit (above 100 µmol/L [1.1 mg/dL] in males and above 90 µmol/L [1.0 mg/dL] in females) in our laboratory, the severity of ARF was scored using "acute on chronic" criteria. In 48 patients, the baseline steady-state plasma creatinine concentration could not be obtained from previous hospital records and was estimated using the Modification of Diet in Renal Disease (MDRD) formula; GFR (mL/min/1.73m^2) = exp(5.228-1.154 x ln(SCr)-0.203 x ln(age)-(0.299 if female)+(0.192 if African-American)) (Levey et al. 1999). The ability of the RIFLE and the Bellomo classifications to predict mortality was tested, and compared with APACHE II (Knaus et al. 1985) and SOFA (Vincent et al. 1996) scores. Hospital mortality rate was recorded.

Study II. This was a cohort study that included 103 adult patients with SIRS from two university hospital ICUs who were prospectively enrolled in the study within 24 h of admission to the ICU. Monocyte expression of histocompatibility leukocyte antigen-DR (HLA-DR), and plasma levels of pro- and anti-inflammatory cytokines (IL-6, IL-8, and IL-10) and their predictive value in prediction of hospital mortality were assessed. Severity of illness was determined by calculating APACHE II score on admission and SOFA score for days 1-3. Mortality rate was assessed 28 days after admission to ICU.

Study III. A prospective cohort of 199 patients (202 treatment episodes) treated in a university hospital ICU was investigated. Serum cystatin C, plasma creatinine, and plasma urea were evaluated as markers of renal function in ARF, and their power in predicting mortality of ARF patients was assessed. Severity of illness was determined by calculating admission APACHE II score and SOFA score daily during the ICU stay. Hospital mortality rate was assessed.

Study IV. This was a prospective, controlled, cross-over study. Sixteen emergency patients who met the inclusion criteria of rhabdomyolysis and plasma myoglobin concentration over 10 000 µg/L, were allocated into two groups after written consent had been obtained. Forced alkaline diuresis was started immediately after allocation and continued throughout the study. HDF, which lasted for four hours, was started in group A immediately after allocation and in group B four hours later. The effect of HDF versus forced alkaline diuresis alone on plasma myoglobin clearance in rhabdomyolysis was studied. The primary outcome measure was the percentual decrease in plasma myoglobin concentration during the intervention. The plasma concentration of myoglobin was plotted against time (0-4 hours) for HDF and forced alkaline diuresis. The area under the curve ($AUC_{0\text{-}4h}$) was

calculated by using the trapezoidal method. The sieving coefficient for myoglobin and the myoglobin clearance rate were determined. The sieving coefficient for myoglobin was calculated from the equation: $S= C_f/C_w$, where C_f represents the concentration of myoglobin in the filtrate. C_w represents the concentration of myoglobin at the membrane surface, which was calculated from the difference in pre- and post-filter concentrations of myoglobin. Myoglobin clearance (K) was calculated by multiplying the sieving coefficient with ultrafiltration rate, which was 10.25 L/h (170.83 mL/min): K= S x 170.83 mL/min. Because of the cross-over design of the study and easily recognizable natures of the two interventions, neither patients nor researchers were blinded. One researcher enrolled the patients in the study and supervised the HDF procedure and another performed the statistical analysis. Urinary alkalization was carried out by the clinician on duty, who was not part of the research team. All other interventions for rhabdomyolysis, except the study interventions, were not allowed. Severity of illness was assessed by calculating APACHE II and SOFA score for the allocation day. The primary analysis was intention-to-treat. All patients who underwent random allocation were analyzed according to their original group assignment. Missing data were handled by imputing values using the group average/last observed response. Fourteen patients remained for the per-protocol analysis since two patients in group A were considered protocol violators.

Study V. This was a cross-sectional cohort study with 703 patients who had received RRT for ARF during 1998-2002 either in an ICU or in an acute RRT unit at a university hospital. The Central Population Registry of Finland confirmed the number of ARF patients alive and living in Finland in June 2003 and again in May 2004. Long-term survival was determined after a median follow-up of 3.9 years, which was defined as the time between the onset of RRT and the date of confirmation of the patient's status (alive or dead) by the Central Population Registry.

The HRQoL of survivors was evaluated after a median follow-up of 2.4 years using a validated Finnish version of a generic, standardized, multidimensional health questionnaire: the EuroQol five dimensions, (EQ-5D) (Brooks R 1996). The survivors received the questionnaire by mail in August 2003. Enclosed was a letter explaining the purpose of the study, a written consent form, and the EQ-5D instrument of HRQoL. The HRQoL of the survivors was then compared with an age- and gender-matched Finnish general population. Table 9 shows the design of the studies.

Laboratory assays

Plasma / serum creatinine (I-V). Plasma creatinine concentrations were analyzed using fully automated enzymatic assays (Hitachi Modular, Roche, Tokyo, Japan). Serum concentrations were measured in Study II and plasma concentrations in other studies. In Helsinki University Central Hospital, the upper normal range limit for plasma creatinine concentration in males was changed in 2004. The upper range limit for plasma creatinine concentration in males was therefore different in Studies I

Table 9. *Design of Studies I-V.*

Study	No of Patients	Design	Interventions	Object
I	668	Prospective, cohort, unselected patients	None	Comparison of ARF-specific scores in prediction of hospital mortality
II	103	Prospective, cohort, SIRS patients	None	Evaluation of IL-6, IL-8, IL-10 and HLA-DR expression in prediction of 28-day mortality
III	199	Prospective, cohort, unselected patients	None	Evaluation of cystatin C in prediction of ARF/hospital mortality
IV	16	Prospective, controlled, cross-over	HDF vs. FAD	Comparison of HDF and FAD in plasma myoglobin elimination rate
V	703	Retrospective, cohort, unselected patients	Assessment of health-related quality of life	Evaluation of long-term survival and quality of life after ARF

ARF=acute renal failure, IL=interleukin, HLA-DR=Histocompatibility leukocyte antigen-DR, HDF=hemodiafiltration, FAD=forced alkaline diuresis.

and III. In Study I, plasma values less than 100 µmol/L were considered normal and in Study III less than 95 µmol/L. In females, plasma values less than 90 µmol/L were considered normal.

Plasma urea (I, III-V). Plasma urea concentrations were analyzed using fully automated enzymatic assays (Hitachi Modular, Roche, Tokyo, Japan). Values less than 10 mmol/L were considered normal.

Plasma concentrations of interleukins 6, 8, and 10 (II). The blood for cytokine analyses was collected into EDTA tubes, centrifuged, and stored at –70ºC until analyzed. Plasma levels of IL-6, IL-8, and IL-10 were determined as duplicates by commercial enzyme immunoassays according to the manufacturer's instructions (CLB, Amsterdam, Netherlands). Laboratory data were collected on the day of admission and two days thereafter.

Monocyte HLA-DR expression (II). The blood for HLA-DR analysis was collected into EDTA tubes, centrifuged, and stored at –70°C until analyzed. For flow cytometry, fresh 100 µL aliquots of the EDTA blood samples were triple-stained at 4ºC with pre-titrated amounts of CD14-FITC, HLA-DR-PE (IgG2a), and CD45-PerCP antibodies. Control samples were stained with CD14-FITC, irrelevant IgG2a-Pe, and CD45-PerCP, accordingly. All antibodies were from Becton Dickinson, San Jose, CA, USA. After incubation, erythrocytes were lysed by the addition of diluted FACS lysing solution (Becton Dickinson), and stained leukocytes were washed with phosphate-buffered saline supplemented with 0.1% NaN3. Samples were analyzed on a

FACsort or FACS calibur flow cytometer using CellQuest software (Becton Dickinson). A total of 5000 events were collected in a live gate combining CD 14-positive events and the monocyte area in a light scatter dot plot. Events collected were analyzed in a FL1/FL2 dot plot. Markers discriminating between negative and positive FL2 events were set to allow for approximately 1% positive events in the control sample. HLA-DR-expressing monocytes were expressed as a percentage of the total number of CD14-positive monocytes. Color compensation was checked on a daily basis using aliquots of normal EDTA blood samples stained with CD3-FITC, -PE, and/or –PerCP. Laboratory data were collected on the day of admission and two days thereafter.

Serum cystatin C (III, IV). Serum cystatin C was analyzed using a fully automated immunonephelometric method (BN II, Dade Behring, Marburg, Germany). Values less than 1.04 mg/L were considered normal. In Study III, serum cystatin C was measured on admission, daily for the first three days, and 5-7 times a week for the rest of the ICU stay. In Study IV, serum cystatin C concentration was measured once before initiation of intervention.

Plasma myoglobin (IV). Arterial plasma myoglobin concentration was measured at allocation and every two hours during the interventions using a fully automated photometric and immunochemical method.

Scoring methods for the severity of illness

1. General (I-V)

To evaluate the general severity of illness, APACHE II (Knaus et al. 1985) and SOFA (Vincent et al. 1996) scores were used. The APACHE II score was calculated on admission (I-III), except in studies IV-V, where it was calculated on the day of allocation and on the day when RRT commenced, respectively. The SOFA score was mainly calculated daily (I, III) or daily for the first three days (II), but in Study IV it was calculated on the day of allocation and in Study V on the day when RRT commenced. In Study I, APACHE II and SOFA scores were used as references for the two ARF-specific scores studied.

2. ARF-specific scores (III)

Scoring of the severity of ARF in Study I was done by two specific scoring methods for ARF: the RIFLE classification and the Bellomo classification. These methods were chosen as they cover a wide range of severities of illness and are therefore both sensitive and specific. Both scoring systems have specific criteria for "acute on chronic" ARF as well. The RIFLE classification defines five stages (Table 2), and the Bellomo classification three stages of ARF (Table 1).

Interventions

The intervention protocol for rhabdomyolysis patients in Study IV was as follows: fluid replacement with NaCl 0.9% 1000mL per hour and urinary

alkalization with NaHCO3 100 mL per hour as soon as the patient was diagnosed with rhabdomyolysis and considered eligible for the study. A RRT catheter (Mahurkar 11.5 Fr) was placed in the right vena jugularis interna. Invasive hemodynamic monitoring was started to maintain a central venous pressure (CVP) of 12-14 mmHg and mean arterial blood pressure of 75 mmHg. When adequate CVP was reached, fluid replacement was reduced to 400 mL per hour and NaCl 0.9% was replaced by NaCl 0.35% and glucose 0.5%. Intravenous furosemide was administered if CVP rose above 14 mmHg to avoid fluid overload. Norepinephrine (2 mg in 100 mL of 0.5% glucose) infusion was initiated if necessary to maintain mean arterial blood pressure of 75 mmHg.

HDF (4008H Fresenius) was delivered using a predilution mode with an FX-100 dialyzer and a bicarbonate-based solution as a replacement. Figure 2 shows the principle of the hemodiafiltration system. Ultrafiltrate (1000 mL in four hours) was replaced to maintain a zero balance. Dalteparin 5000 ky was given as a bolus for anticoagulation before HDF was started, and an extra bolus of 2500 ky was given during HDF if necessary. Anticoagulation activity was monitored by measuring arterial anti-fXa every two hours during HDF. The total amount of filtrated myoglobin was measured from the 161 L of filtrate at the end of HDF.

FAD was carried out by administering sodium bicarbonate 1.4% 50-100 mL per hour to maintain urine pH of at least 7.5 and urine output above 400 mL per hour. Urine alkalization was continued also during HDF.

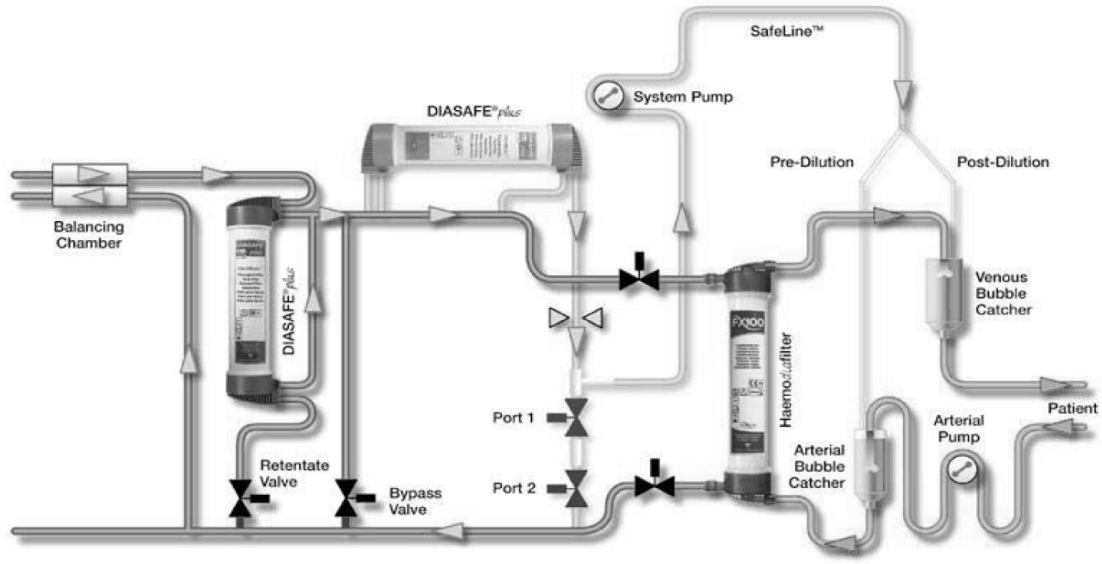


Figure 2. *Fresenius 4008H hemodiafiltration system. Printed with permission from Fresenius Medical Care.*

Outcome measures

1. MORTALITY (I-III, V)

Short-term mortality (I-III). These comprised 28-day mortality (II) and hospital mortality (I, III).

Long-term mortality (V). The Central Population Registry of Finland, which maintains a record of all deaths and current addresses of Finnish citizens, confirmed the number of ARF patients alive and living in Finland in June 2003 and again in May 2004. The follow-up time was defined as the period between the onset of RRT and the date of confirmation of the patient's status (alive or dead) by the Central Population Registry. This resulted in a follow-up time for mortality of 1.4-6.4 (median 3.9, interquartile range 2.5-5.0) years.

2. QUALITY OF LIFE (V)

The EuroQol five dimensions (EQ-5D), a generic, standardized, multidimensional, self-administered instrument, was used to measure HRQoL in Study V. The EQ-5D includes five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) evaluated on a 1-3 scale. These dimensions are described in detail in Table 16 (page 63). The instrument utilizes a set of population-based preference weights to calculate a single index score representing the overall HRQoL, which facilitates comparison with the age- and gender-matched general population. The EQ-5D instrument was chosen for this study because of its multidimensionality and subjective expression of a patient's health, both widely accepted criteria for HRQoL measurement. In 2002, the EQ-5D was assessed as suitable for measuring HRQoL in critical care at the Brussels Roundtable meeting (Angus et al. 2003). The EQ-5D instrument also includes a visual analog scale (VAS) for self-rating of patients' health, ranging from 0 to 100 (representing the worst and best states imaginable). Respondents rate their health state by drawing a line to the appropriate point on the VAS scale. For HRQoL, the follow-up time was between 0.6 and 5.6 (median 2.4, interquartile range 1.2-3.8) years in Study V.

3. QUALITY-ADJUSTED LIFE- YEARS (V)

In Study V, quality-adjusted survival was calculated for the first year by multiplying the EQ-5D index score by the one-year survival, and for the entire survival period by multiplying the EQ-5D index score by the total survival time. The costs per quality-adjusted life-year were calculated using the total costs of hospital treatment per patient. Direct secondary healthcare costs to the provider were obtained from the Ecomed® clinical patient-level costing and analyzer system (Datawell Ltd., Finland), where all cost data concerning treatment of individual patients in the hospital are stored. For patients treated before the year 2000, the total costs of hospital treatment were approximated using the information for the year 2000. Indirect costs (e.g. post-hospitalization costs or increased costs for basic healthcare) were not included in the calculation. For intermittent RRT, the costs of treatment were summed directly from hospital billing records. For CRRT, the costs of treatment were calculated by combining the costs of dialysis equipment, fluids, filters, venous access

catheters, etc., and the wages of nursing staff.

4. PREDICTION OF OUTCOME (I-III)

The development process of validating predictive tools has been reviewed by Ruttimann (1994). For model identification, the association of possible significant risk factors with outcome is first tested by univariate data analysis. Receiver operating characteristic (ROC) analysis is recommended to test the model's discriminative power for the selected outcome. For model calibration, multivariate data analysis, such as logistic regression analysis, is used.

In Studies I-III, where predictive variables for mortality were tested, the study population consisted of an unselected heterogeneous cohort population of ICU patients, as recommended by the Evidence-Based Medicine Working Group (Laupacis et al. 1994). The Mann-Whitney U-test and X^2-test, were used as appropriate, to identify factors associated with mortality. Variable's power to discriminate between survivors and nonsurvivors was tested by ROC analysis. Forward stepwise logistic regression analysis was used to test the variable's ability to independently predict mortality. Likelihood ratios for hospital mortality were determined in Study I as recommended by the Evidence-Based Medicine Working Group (Laupacis et al. 1994).

Statistical methods

The amount of missing data was determined in all studies. A p-value of less than 0.05 was considered significant, except in multiple comparisons, where Bonferroni corrections were calculated. Statistical analysis was performed using SPSS® 10.1.3 and 12.0.1 for Windows (SPSS Inc., IL, USA).

SAMPLE SIZE CALCULATION (I-V)

In Studies I and V, a sample of approximately 700 consecutive patients were collected. The appropriate sample size was approximated based on clinical experience. In Studies II and III, an adequate sample size was determined based on previous mortality rates and prevalence of ARF in the ICU. In Study IV, power analysis was performed to estimate an adequate sample size for revealing a clinically significant difference in plasma myoglobin decrease between the two treatment arms with a probability of 95% and a power of 80%. The decrease in plasma myoglobin concentration was approximated to be 12 000 µg/L during HDF and 6000 µg/L during FAD with a standard deviation of the difference of 6000 µg/L. As a result, 15 patients were approximated to be sufficient, and final sample size was 16 patients.

DATA CONSIDERATIONS (I-V)

The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to evaluate the variables for normality. Data were not normally distributed in any of the studies, and thus, nonparametric tests were applied. A normalization procedure was carried out by 1/X normalization for plasma myoglobin concentrations and by logarithmic normalization for urine output for the analysis of variance in Study IV.

TESTS FOR COMPARING POPULATIONS

X^2-test (I-V): X^2-test is used to test differences between two categorical variables. Here, it was used to compare patients' demographic data. Moreover, in Study I, X^2-test was applied to determine whether mortality differed in different stages of ARF.

Fisher's exact test (V): Fisher's exact test was used instead of X^2-test when the expected number of cases in any variable classes was less than five. The one-year mortality rates of patients treated in the ICU versus in the hospital wards were compared by Fisher's exact test in Study V.

Mann-Whitney U-test (I-V): The Mann-Whitney U-test was used to compare continuously distributed data of two independent populations. It was also used to test patients' demographic data in all studies. Moreover, it was applied to evaluate differences between patients with and without ARF in studies II and III, AUCs (0-4 h), sieving coefficients for myoglobin, and myoglobin clearance rates in Study IV, and the HRQoL of patients treated in ICU versus in the acute dialysis unit in Study V.

Wilcoxon signed-rank test (V): In Study V, the EQ-5D index scores of the study population were compared with those of the age- and gender-matched Finnish general population by the Wilcoxon-signed rank test, which is used to compare differences between paired groups if data distribution is categorical or continuous.

Kruskal-Wallis test (V): The Kruskal-Wallis test was used to compare continuously distributed data of several independent populations. In Study V, the study population was divided into three age groups (≤50 years, 51-65 years, >65 years), and the Kruskal-Wallis test was used to compare EQ-5D scores and VAS scores between age groups.

Kendall's W-test (I): Kendall's W-test was applied to compare the distributions of several related samples. It was used to test the similarity of an individual patient's distribution across the ARF severity stages in study I. Coefficient W (Wa) measures concordance and may vary from 0 to 1, value 0 indicating total disagreement between distributions and value 1 total agreement between distributions.

Analysis of variance (ANOVA) (IV): ANOVA was used in Study IV to test the hypothesis that the means for the study groups come from the same sampling distribution of means. Repeated measures ANOVA included plasma myoglobin concentrations over time, treatment period, and intervention group as variates, and total urine output for 12 hours as a covariate. The presence of a significant carry-over effect was excluded by including an intervention period in the ANOVA procedure.

TESTING PREDICTIVE ABILITY

Sensitivity and specificity (I): Sensitivity and specificity for mortality were calculated in Study I for each separate stage of the RIFLE and Bellomo classifications (Table 10).

Sensitivity was calculated as follows: A / (A+C).

Specificity was calculated as follows: D / (D+B).

Table 10. *Two-way table for calculation of sensitivities, specificities, and likelihood ratios in Study I.*

	Number of deceased patients	Number of surviving patients
Number of patients fulfilling the criteria	A	B
Number of patients not fulfilling the criteria	C	D

Likelihood ratios (I): In Study I, positive likelihood ratios for death, representing the likelihood of death divided by the likelihood of survival, were calculated as follows: sensitivity / (1-specificity). Likelihood ratios were calculated for each stage of the RIFLE and Bellomo maximum scores during the first three days in the ICU. The total likelihood for death at each stage was determined by multiplying the likelihood for death, without knowing the renal status of the patient, with the calculated likelihood ratios.

Logistic regression analysis (I-III, V): In studies I-III and V, independent predictors for mortality were tested by logistic regression analysis since the outcome variable was dichotomous. In Study I, the analysis included admission day scores for RIFLE, Bellomo, APACHE II, and SOFA, and maximum scores for the first three days for RIFLE and Bellomo scores. In Study II, the analysis included admission day laboratory values. In Study III, the analysis included patient's age, day 1 and maximum serum cystatin C and plasma creatinine concentrations, APACHE II and SOFA scores, need for corticosteroid therapy, and development of ARF. In Study V, the one-year mortality of patients treated in the ICU versus in the hospital wards and of patients treated in different years (1998-2002) was analyzed. APACHE II and SOFA scores, age, sex, and mode of RRT were used as variates, and treatment unit and treatment year as covariates in the analysis.

Receiver operating characteristic (ROC) analysis (I-III): In ROC analysis, the results are expressed as an area under the curve (AUC), where the curve represents the relationship between sensitivity and (1-specificity) (Hanley et al. 1982). It can also be expressed as the relationship between the fraction of true positives and the fraction of false positives. The predictive power of a variable is expressed as an AUC; the greater the AUC, the better the predictive ability. An AUC value of 0.5 represents a predictive ability equivalent to tossing a coin or a 50-50 chance. In studies I-III, the power of the studied variables to discriminate between survivors and nonsurvivors was determined by ROC analysis, where mortality was used as a dependent variable; and the investigated variables as independent variables. In Study II, the results of the Mann-Whitney U-test were used to select variables for the ROC analysis; only variables with significant differences between ARF and nonARF patients were selected. These variables included monocyte HLA-DR expression on days 1-3, plasma levels of IL-6 on days 2 and 3, plasma levels of IL-8 on days 1-3, and plasma levels of IL-10 on day 2.

OTHER TESTS

Z-scores (V): Z-scores are calculated from the mean values of a study population and a standard population. It describes the difference in means of the study population and the standard population as the number of standard deviations. Z-scores in Study V were calculated for EQ-5D index scores and VAS scores.

Spearman's correlation (II-III, V): Spearman's correlation coefficients were computed to examine the linear relationships between variables in studies II and III. In Study II, the correlation between monocyte HLA-DR expression and interleukin plasma values on day 1 was tested. In Study III, the correlations between serum cystatin C concentrations and plasma creatinine and urea concentrations on days 1-10 were tested. Spearman's correlation coefficients were computed to identify correlations between variables and HRQoL.

Kaplan-Meier test (V): The mortality over time of ARF patients receiving RRT during the treatment period was investigated by Kaplan-Meier survival analysis in Study V.

Ethical aspects

The study protocols were approved by the institutional Ethics Committee. Informed consent was obtained from each patient or their next of kin in studies IV and V. The Ethics Committee waived the need for informed consent in studies I-III. In Study IV, although the effect of FAD on myoglobin removal from plasma has not been proven, comparison of HDF with no treatment was considered unethical. The effect of HDF was therefore compared with the best available clinical practice, as recommended for all new treatments in clinical studies in critically ill patients.

5. RESULTS

5.1. Prevalence of acute renal failure (I-IV)

Table 11. *Patients in Study I (n=658) stratified according to the RIFLE and Bellomo classifications (maximum points during the whole ICU period).*

RIFLE		Bellomo	
No ARF	316 / 658 (48%)	**No ARF**	520 / 658 (79%)
Risk	168 / 658 (26%)	**ARI**	85 / 658 (13%)
Injury	100 / 658 (15%)	**ARFS**	16 / 658 (2%)
Failure	74 / 658 (11%)	**SARFS**	37 / 658 (6%)

ARF= acute renal failure, RIFLE= risk, injury, failure, loss of renal function, end-stage renal disease, ARI= acute renal injury, ARFS= acute renal failure syndrome, SARFS= severe acute renal failure syndrome.

According to the results of Studies I and III, the incidence of ARF (defined as stage "Failure" according to the RIFLE classification) in a heterogeneous critically ill patient population during the whole ICU stay was 128/857 patients (15%, 95% CI 13-17%): 74/658 patients (11%, 95% CI 9-14%) in Study I and 54/199 patients (27%, 95% CI 21-34%) in Study III. Incidence of ARF in patients with SIRS / sepsis was determined in Study II, where the incidence for ARF was 36/103 (35%, 95% CI 26-45%). The incidence of ARF in patients with severe rhabdomyolysis was 6/16 patients (37.5% 95% CI 18-62%) (Study IV). The distribution of patients in Study I across the separate stages of renal dysfunction according to the RIFLE and Bellomo definitions is presented in Table 11.

5.2. Cytokines and monocyte human histocompatibility leukocyte antigen-DR (HLA-DR) expression in acute renal failure (II)

In critically ill patients with SIRS/sepsis, the plasma concentrations of several pro- (IL-6, IL-8) and anti-inflammatory cytokines (IL-10) were significantly higher in ARF than nonARF patients. In addition, the amount of HLA-DR-expressing monocytes was significantly lower in ARF than nonARF patients on days 2 and 3 (Table 12). The ability to predict ARF by ROC analysis was from poor to moderate for the studied interleukins and monocyte HLA-DR expression (day 1 AUCs: IL-6: 0.641, Il-8: 0.771, IL-10: 0.647, and HLA-DR expression: 0.420).

Table 12. *Plasma cytokine levels and monocyte HLA-DR expression in patients with (ARF) and without (nonARF) acute renal failure in Study II.*

		ARF patients (n=36)	nonARF patients (n=67)	p
IL-6 (pg/mL)	Day 1	614 (331-2000)	433 (124-1011)	NS
	Day 2	365 (60-1000)	88 (31-601)	<0.05
	Day 3	162 (31-1000)	51 (18-147)	<0.05
IL-8 (pg/mL)	Day 1	91 (43-246)	28 (10-44)	<0.001
	Day 2	86 (21-206)	21 (8-45)	<0.001
	Day 3	87 (18-159)	21 (7-38)	<0.001
IL-10 (pg/mL)	Day 1	12 (19-47)	7 (0-19)	<0.05
	Day 2	7 (5-23)	0 (0-7)	<0.001
	Day 3	5 (0-12)	0 (0-6)	<0.05
HLA-DR (%)	Day 1	69 (51-87)	79 (62-92)	NS
	Day 2	64 (43-80)	79 (60-91)	<0.01
	Day 3	75 (44-83)	83 (75-93)	<0.01

ARF=acute renal failure, IL=interleukin, HLA-DR=Human histocompatibility leukocyte antigen-DR, NS=not significant.

5.3. Serum cystatin C in acute renal failure (III)

In a heterogeneous ICU population, serum cystatin C concentrations measured throughout the ICU period ranged from 0.4 to 9.0 mg/l in patients who developed ARF at some point during their stay. In patients who did not develop ARF during their ICU period, serum cystatin C concentrations ranged from 0.3 to 3.9 mg/l. The development of serum cystatin C and plasma creatinine values is shown in Figure 3.

Serum cystatin C concentrations correlated in a clinically significant manner with both plasma creatinine and plasma urea concentrations (Spearmans's correlation coefficients for days 1-10 were between 0.72 and 0.86, $p<0.001$) and inversely with the GFR estimated by the MDRD formula (Spearman's correlation coefficients for days 1-10 between -0.74 and -0.87). The correlation between the estimated GFR and serum cystatin C concentration on day one is shown in Figure 4. Based on the figure, a cut-off value of 1.5 mg/L for serum cystatin C was estimated, as values above this threshold were clearly associated with a decrease in GFR to less than 50 mL/min/1.73m^2. On the other hand, a normal serum cystatin C concentration did not sort out all patients with decreased GFR.

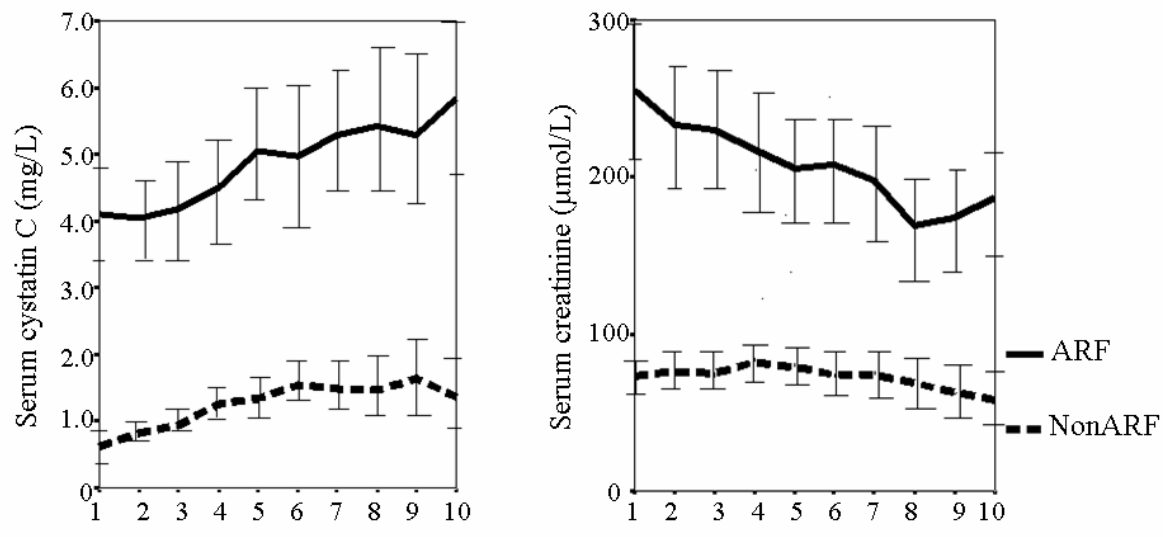


Figure 3. *Development of serum cystatin C and plasma creatinine concentrations in patients with and without ARF on days 1-10 in Study III.*

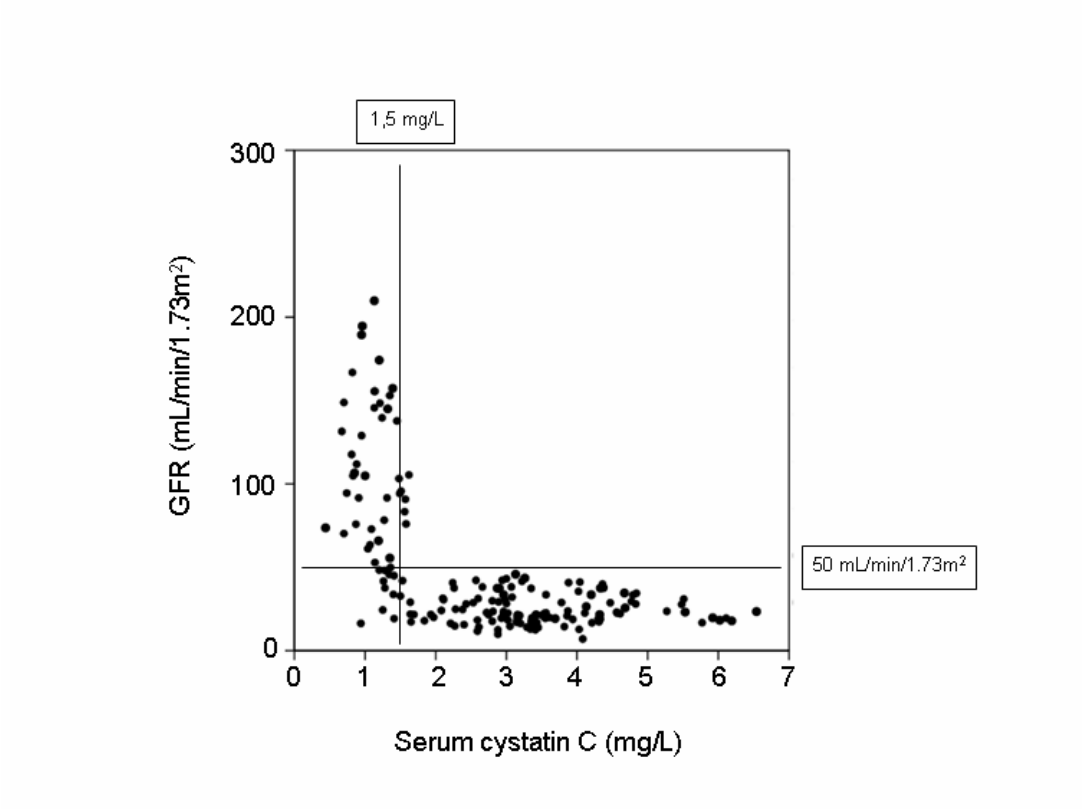


Figure 4. *Simultaneous values of estimated (MDRD) glomerular filtration rate (GFR) and serum cystatin C in patients on days 1-10 in Study III.*

In 29 patients, plasma creatinine concentration was normal on admission, rising later to an abnormal level. The abnormal level was reached on day 3 (median, range 2-11 days). In these 29 patients, serum cystatin C also exceeded the reference range within a median of 3 (range 1-6) days. The time interval for the creatinine increase was similar to that of the cystatin C increase (p=0.40, Mann-Whitney U-test). Plasma creatinine remained normal throughout the study period in 80 patients, 28 (35%) of whom showed increased serum cystatin C. In these patients, the median for the highest serum cystatin C concentration was 1.29 (interquartile range 1.15-1.65) mg/L. Serum cystatin C remained normal throughout the study period in 58 patients, 7 (12%) of whom had increased plasma creatinine. In these patients, the median for the highest plasma creatinine concentration was 98 (interquartile range 96-102) μmol/L. ROC analysis showed excellent predictive power in the prediction of ARF for days 1-3 serum cystatin C (AUCs 0.885, 0.893, and 0.901, respectively).

Treatment with corticosteroids increased serum cystatin C concentrations in nonARF patients. However, in ARF patients, a similar effect was not found. In nonARF patients, the medians for cystatin C concentrations in the first three days were 0.92, 1.07, and 1.15 (treated with corticosteroids) vs. 0.78, 0.85, and 0.92 (no corticosteroids) (p=NS). In ARF patients, the respective figures were 2.50, 2.60, and 2.51 vs. 2.75, 2.32, and 3.02 (p=NS).

5.4. Impact of hemodiafiltration vs. forced alkaline diuresis on plasma myoglobin levels in rhabdomyolysis (IV)

The percentual elimination of myoglobin from the circulation during HDF was significantly greater than during FAD ($p<0.05$). When absolute plasma concentrations were compared, the difference in the elimination of myoglobin was not statistically significant, although a trend towards faster myoglobin elimination during HDF was present. Table 13 shows the elimination of myoglobin in percentual values and in absolute plasma concentrations, and the AUCs for plasma myoglobin concentrations during HDF vs.FAD.

ANOVA revealed no significant differrences in plasma myoglobin concentration over time between the treatment arms. Also, no significant carry-over effect was present. Complete case analysis yielded a mean difference in myoglobin clearances of 6085 (95% CI 343-11828, median 4040, and interquartile range -1257-11065) μg/l in four hours during HDF vs. FAD. The mean total amount of filtrated myoglobin at the end of HDF was 58.4 (95% CI 21.9-94.9, median 27.9, and interquartile range 19.5-87.4) mg. Mean creatinine clearance in group A was 0.30 (median 0.04, 95% CI -0.39-0.99, interquartile range 0.01-0.45) mL/s/1.73m^2, and in group B 0.69 (median 0.41, 95% CI 0.07-1.31, interquartile range 0.17-1.20) mL/s/1.73m^2. No significant difference was found between the groups.

Total urine output during the whole eight-hour study period was significantly lower in the group A than in group B; by

Table 13. *Decrease in plasma myoglobin concentration (P-Myogl) and areas under curve (AUC) during hemodiafiltration (HDF) and forced alkaline diuresis (FAD) in Study IV in patients with rhabdomyolysis. The results of intention-to-treat (ITT, n=16) and complete case analysis (n=14) are shown as mean (95% confidence intervals).*

	ITT, using group average	ITT, using last observation	Complete case analysis
Percentual decrease in P-Myogl during HDF	28.3 (18.9-37.7)*	26.4 (16.2-36.5)*	28.1 (18.0-38.2)*
Percentual decrease in P-Myogl during FAD	13.4 (7.0-19.9)*	12.5 (5.6-19.3)*	14.2 (6.9-21.6)*
Decrease in P-Myogl during HDF (µg/L)	9819 (3845-15 794)	8227 (2561-13 893)	9731 (3672-15 791)
Decrease in P-Myogl during FAD (µg/L)	4804 (1392-8217)	3190 (1035-5345)	3646 (1260-6032)
AUC for HDF (µg/L/4h)	52 642 (24 854-80 430)	54 456 (26 211-82 700)	51 997 (22 141-81 853)
AUC for FAD (µg/L/4h)	52 086 (23 689-80 484)	57 469 (28 421-86 518)	53 123 (20 134-86 111)

*$p<0.05$.

complete case analysis, medians 93 mL vs. 733 mL (interquartile ranges 51-484 mL and 273-2181 mL), respectively ($p=0.03$). Mean urine output during HDF was also lower than during FAD 237 mL vs. 1664 mL, (medians 160 mL and 203 mL, 95% CIs 9-465 mL and 398-2931 mL, interquartile ranges 36-258 mL and 29-564 mL), but the difference was not significant. Mean urine pH of the study population during the four hours of FAD was 6.2 (median 6.0, 95% CI 5.8-6.5, interquartile range 5.9-6.3). It was the same in both groups.

5.5. Mortality in acute renal failure (I-III, V)

Short-term mortality (I-III)

According to the results of Studies I and III, the hospital mortality rate for ARF (defined as RIFLE stage "Failure") in a heterogeneous critically ill patient population was 34% (43/128 patients): 17/74 patients (23%) in Study I and 26/54 patients (48%) in Study III. The 28-day mortality rate in ARF patients with SIRS/sepsis determined in Study II was 8/36 patients (22%). Taken together, the overall short-term mortality rate in ICU patients with ARF was 31% (51/164 patients). In patients without ARF the short-term mortality rate was 13% (101/808 patients): 59/584 patients (10%) in Study I, 12/67 patients (18%) in Study II, and 28/145 patients (28/148 treatment episodes) (19%) in Study III. The difference in short-term mortality rates between patients with and without ARF was significant by the Mann-Whitney U-test ($p<0.001$). Hospital mortality differed significantly in the different stages of ARF by the X^2-test in the Study I ($p \leq 0.05$, Figure 5).

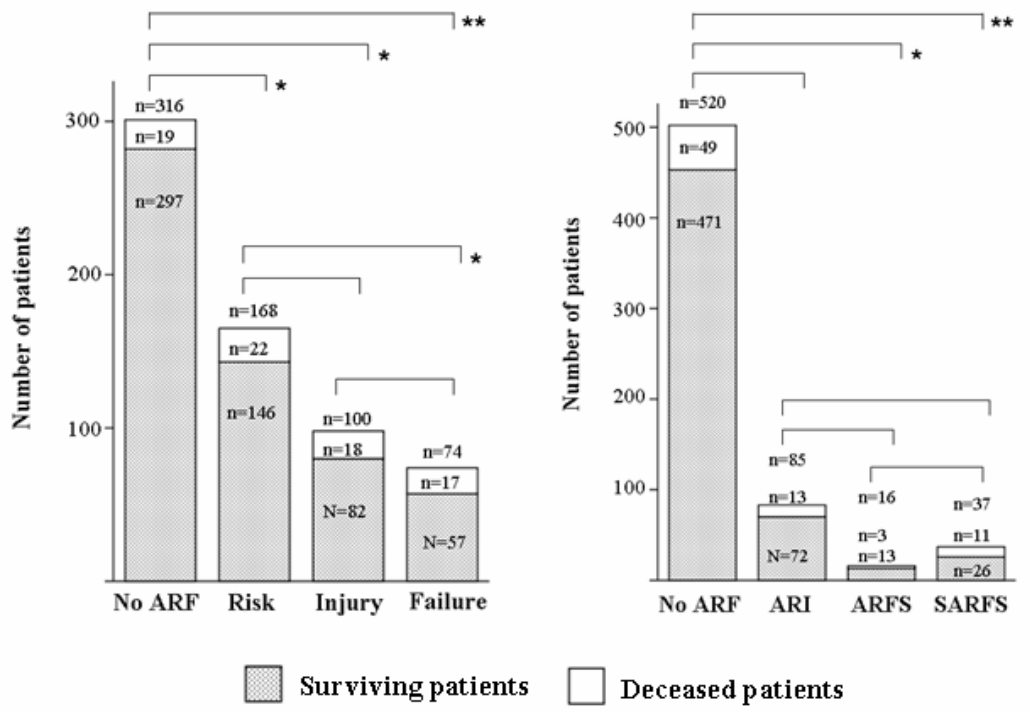
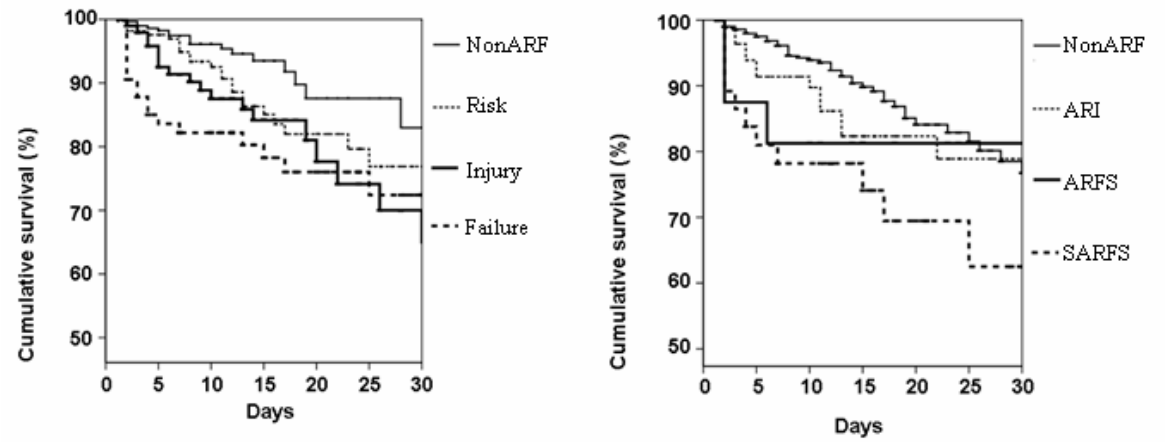


Figure 5. *Hospital mortality in Study I stratified according to the separate stages of ARF. ARF= acute renal failure, ARI= acute renal injury, ARFS= acute renal failure syndrome,SARFS= severe acute renal failure syndrome. p<0.05 is marked * and p<0.001 is marked **.*

Survival of patients over time is presented in Figure 6. Sensitivities, specificities, and likelihood ratios for death are presented in Figure 7. Multiplying overall hospital mortality rate with the likelihood ratios resulted in total likelihoods for death of 17%, 22%, and 26% for the RIFLE stages of Risk, Injury, and Failure, respectively, and 21%, 31%, and 36% for the Bellomo stages ARI, ARF, and SARFS, respectively.

Long-term mortality (V)

In the Study V, the long-term mortality of ARF patients needing RRT during hospitalization was 41% (277/681) in 28 days, 57% (387/681) in one year, and 70% (120/172) in 5 years (Figure 8). Nonsurvivors were older than survivors: 64 (interquartile range 53-73) years vs. 55 (interquartile range 43-67) years (p<0.001). The one-year mortality rate differed significantly between the patients treated in the ICU (57%, 317/553) and patients treated in the hospital wards (47%, 70/150) (p<0.05). No significant differences were present in the one-year mortality rate of patients treated in different years (1998-2002) (p=NS).



	0 days	10 days	20 days	30 days
Number of patients in hospital	658	406	154	93
Number of deceased patients	0	43	66	73

Figure 6. *Survival of patients over time stratified according to the separate stages of acute renal failure (ARF) in Study I. ARI= acute renal injury, ARFS= acute renal failure syndrome, SARFS= severe acute renal failure syndrome.*

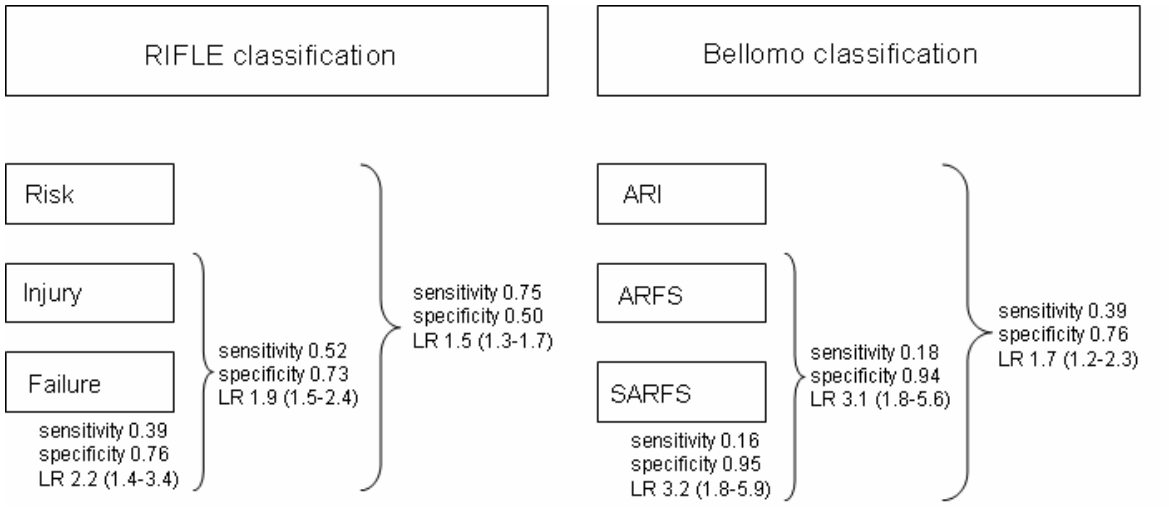
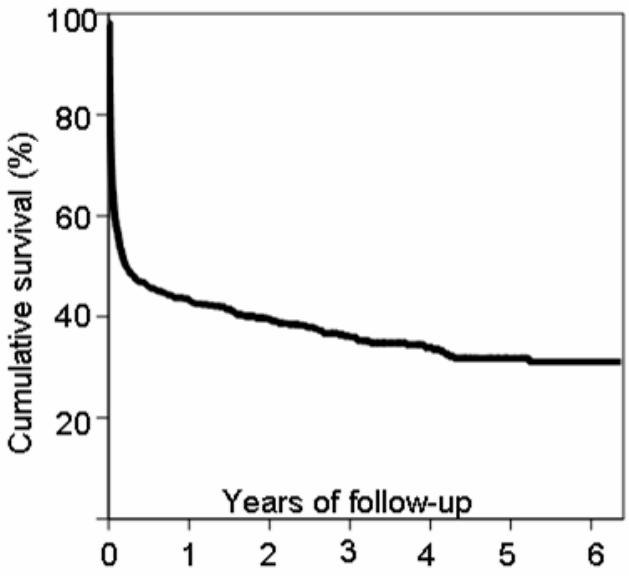


Figure 7. *Sensitivities, specificities, and likelihood ratios (LRs) for death at each stage of acute renal failure (ARF) according to the RIFLE and Bellomo classifications (Study I). RIFLE= risk, injury, failure, loss of renal function, end-stage renal disease, ARI= acute renal injury, ARFS= acute renal failure syndrome, SARFS= severe acute renal failure syndrome.*



Years of follow-up	1	2	3	4	5	6
Number of patients in follow-up	681	586	457	332	172	40
Number of deceased patients	387	364	300	223	120	28

Figure 8. *Long-term survival of acute renal failure patients in Study V.*

5.6. Prediction of mortality in acute renal failure (I-III)

Scoring methods for severity of illness (I)

1. ARF-SPECIFIC SCORING METHODS (I)

Logistic regression analysis revealed that the maximum RIFLE score for the first three days was an independent predictor of hospital mortality. The ROC analysis showed only moderate power in discriminating hospital mortality for both ARF-specific scoring methods studied, AUCs varying from 0.581 to 0.653 (Table 14). Secondary analysis with all 683 treatment episodes revealed no significant differences in the results.

Table 14. *Predictive power for hospital mortality of the ARF-specific severity-of-illness scoring methods in Study I.*

Scoring method		AUC	95% CI
RIFLE classification:	day one	0.630	0.558 - 0.701
	max. score for the first 3 days	0.653	0.588 - 0.719
Bellomo classification:	day one	0.581	0.497 - 0.664
	max. score for the first 3 days	0.587	0.514 - 0.660

ARF= acute renal failure, RIFLE= risk, injury, failure, loss of renal function, end-stage renal disease, AUC= area under curve.

2. General severity-of-illness scoring methods (I-III)

The ability of general severity-of-illness scoring methods to independently predict short-term mortality was tested in Studies I-III using scores on the day of admission to ICU. The day 1 SOFA score appeared as an independent predictor of hospital mortality in Studies I and III, but not as an independent predictor of 28-day mortality in Study II. The APACHE II score was as an independent predictor of 28-day mortality in Study II and hospital mortality in Study III, but neither in Study I. However, in a secondary analysis with all 683 treatment episodes, the results changed and admission APACHE II score was as an independent predictor of hospital mortality in Study I as well. When the three study populations were combined to form one large study population, both APACHE II and SOFA scores for day 1 appeared to predict short-term (hospital or 28-day) mortality independently.

In Study I, also the discriminative powers for hospital mortality of the admission-day APACHE II and SOFA scores were calculated. The AUCs were 0.703 (95% CIs 0.637 - 0.769) and 0.725, (95% CI 0.657 - 0.794), respectively. In Studies II and III, the APACHE II and SOFA scores were not included in the original ROC analysis. However, we determined the AUCs afterwards. For the APACHE II score, the AUCs were 0.795 (95% CI 0.590-0.779) and 0.681 (95% CI 0.601-0.761), respectively. For SOFA score the AUCs were 0.741 and 0.648 (95% CIs 0.630-0.853 and 0.557-0.740, respectively). Furthermore, total AUCs for the general severity-of-illness scoring methods for all three studies was determined. For admission-day APACHE II score, the total AUC was 0.687 (95% CI 0.641-0.732), and for admission-day SOFA score 0.722 (95% CI 0.675-0.769).

Laboratory tests (II, III)

1. Serum concentrations of interleukins 6, 8, and 10 (II)

Forward stepwise multiple logistic regression analysis in Study II revealed that only the admission IL-8 value was independently associated with 28-day mortality. The association was lost,

however, if APACHE II was included in the analysis. The ability of the interleukins to predict mortality among ARF patients was evaluated using ROC analysis. The analysis showed moderate discriminative power in prediction of survival only for day 2 plasma levels of IL-6 and IL-10 (AUCs 0.703 and 0.749, respectively).

2. Monocyte HLA-DR expression (II)

In forward stepwise multiple logistic regression analysis, HLA-DR expression was found not to be independently associated with 28-day mortality. Furthermore, it showed poor predictive power for mortality in ARF patients in ROC analysis: AUCs for monocyte HLA-DR expression were 0.630 (standard error (SE) 0.112) on day 1, 0.602 (SE 0.321) on day 2, and 0.644 (SE 0.150) on day 3.

3. Serum cystatin C concentration (III)

Regarding hospital mortality in patients with ARF, ROC analysis showed only weak predictive power for serum cystatin C in Study III. The AUC for day 1 serum cystatin C was 0.624. Forward stepwise multiple logistic regression analysis revealed that serum cystatin C was not an independent predictor of hospital mortality.

4. Plasma creatinine concentration (III)

Only weak predictive power for plasma creatinine concentration regarding hospital mortality was found in Study III. The AUC for plasma creatinine concentration was 0.598. However, forward stepwise multiple logistic regression analysis revealed that admission plasma creatinine concentration was an independent predictor of hospital mortality (p=0.01) in this study.

5.7. Quality of life after acute renal failure (V)

Health-related quality of life (V)

In Study V, of the 229 survivors in 2003 whose address was confirmed by the Central Population Registry, 153 (67%) returned the EuroQol five dimensions (EQ-5D) questionnaire for health-related quality of life including the visual analog scale (VAS) for self-perceived health. The EQ-5D index score of the study population was significantly lower than the EQ-5D index score of the age- and gender-matched general population (median 0.68, interquartile range 0.53-0.85) vs. (median 0.86, interquartile range 0.83-0.88), $p<0.001$. However, the VAS score was slightly higher in the study group than in the age- and gender-matched general population (70.0 (54.8-84.0) vs. 69.5 (67.8-78.1), $p<0.05$). Patients in the three age groups (≤50 years, 51-65 years, >65 years) did not differ from one another regarding EQ-5D index score, VAS score, gender, length of treatment or follow-up, stay in ICU, or Z-score. However, the EQ-5D index score and the Z-score for the age groups differed significantly from those of the age- and gender-matched general population (Table 15).

Table 15. *Health-related quality of life (HRQoL) of the study population (Study V) measured by the EuroQol (EQ-5D) index and the visual analogue scale (VAS) and compared with the age- and gender-matched (Finnish) general population by Z-scores. The EQ-5D and VAS scores are presented as medians (interquartile ranges), and the Z-scores as means.*

	EQ-5D index score	**VAS score**
≤50 years (n=42)	0.69 (0.51-0.85)**	81.5 (56.3-90.0)*
General population (Z-score)	0.93 (5.1**)	84.4 (3.1)
51-65 years (n=56)	0.69 (0.52-0.84)**	68.5 (51.0-80.0)
General population (Z-score)	0.86 (15.0**)	69.5 (1.4)
>65 years (n=55)	0.65 (0.53-0.80)**	70.0 (53.8-79.3)
General population (Z-score)	0.81 (3.5**)	65.7 (0.3)
Whole group (n=153)	0.68 (0.53-0.85)**	70.0 (54.8-84.0)*
General population (Z-score)	0.86 (3.4**)	69.5 (0.7)

**p<0.05, **p<0.0001*

Age, follow-up time, treatment modality, length of RRT, number of RRT treatments, APACHE II score, SOFA score, and EQ-5D score of the age- and gender-matched general population did not correlate with the EQ-5D index score (correlation coefficients –0.06, -0.00, 0.09, -0.08, -0.06, -0.02, -0.01, and 0.05, respectively, NS). The respondents' detailed answers to the five dimensions of the EQ-5D are presented in Table 16.

Quality-adjusted life-years and costs of treatment (V)

Quality-adjusted survival was investigated in Study V, where 15 quality-adjusted life-years per 100 patients was found for ARF patients in the first year. Including the entire survival time in the analysis did not increase the number of quality-adjusted life-years. The total costs of hospital treatment were 28 000 (22 000-37 000) € per patient, 222 000 (41 000-1 610 000) € per quality-adjusted life-year for the first year and 222 000 (14 000-1 610 000) € per quality-adjusted life-year for the entire survival period. At the same time the cost for RRT per quality-adjusted life-year was 25 000 (2000–191 000) €.

Table 16. *EuroQol five dimensions (EQ-5D) health questionnaire and distribution of responses (n=153) in Study V.*

	Number of patients (%)
Mobility	
I have no problems in walking about.	73 (48)
I have some problems in walking about.	74 (48)
I am confined to bed.	6 (4)
Self-care	
I have no problems with self-care.	115 (75)
I have some problems washing or dressing myself.	29 (19)
I am unable to wash or dress myself.	9 (6)
Usual activities (e.g. work, study, housework, family, or leisure activities)	
I have no problems with performing my usual activities.	74 (48)
I have some problems with performing my usual activities.	64 (42)
I am unable to perform my usual activities.	15 (10)
Pain/Discomfort	
I have no pain or discomfort.	68 (44)
I have moderate pain or discomfort.	75 (49)
I have extreme pain or discomfort.	10 (7)
Anxiety/Depression	
I am not anxious or depressed.	107 (70)
I am moderately anxious or depressed.	45 (29)
I am extremely anxious or depressed.	1 (1)

6. DISCUSSION

6.1. Incidence of acute renal failure (I-IV)

The incidence of ARF in these studies varied from 11% to 37.5%. This is slightly higher than in previous studies on ARF, which have reported figures between 5% and 25% in patients admitted to ICUs, depending on the patient population and the severity of illness required to meet the definition of ARF (Groeneveld et al. 1991; Brivet et al. 1996; de Mendonca et al. 2000; Metnitz et al. 2002; Uchino et al. 2005). Moreover, the incidence of ARF in a heterogeneous ICU patient population varied considerably; also among studies where similar definitions of ARF were used (I and III). This might be explained by the much larger proportion of septic patients in Study III (20% vs. 7%), as sepsis is known to have the highest occurrence rate for ARF among critically ill patients, up to 50% (Brivet et al. 1996; Uchino et al. 2005). Confirmation of the high incidence of ARF in septic patients was provided by Study II, where the occurrence rate of ARF in patients with SIRS/sepsis was 35%. However, in this study the degree of illness required for the diagnosis of ARF was less severe than in Studies I and III. Contradicting previous reports, the highest incidence for ARF (37.5%) was found in patients with severe rhabdomyolysis. Study IV had very strict inclusion criteria, resulting in a highly selected patient population and the sample size was not designed to detect differences in the incidence of ARF.

In Study I, the RIFLE criteria for ARF were fulfilled in approximately twice as many patients as the Bellomo criteria. The distribution of patients according to the RIFLE criteria was inconsistant with an earlier study on the subject (Risk: 26% vs. 8%, Injury: 15% vs. 22%, Failure: 11% vs. 22%, and Loss + End-Stage Renal Disease: 0% vs. 9%) (Bell et al. 2005). However, the basic design of the studies differed, as the RIFLE definition was used in different ways. The distribution of patients in the separate stages of ARF according to the Bellomo classification was roughly similar to the distribution reported earlier (ARI: 13% vs. 18%, ARFS: 2% vs. 6%, and SARFS: 6% vs. 4%) (Ostermann et al. 2005). The small number of patients in the ARFS stage in our study reflects the tendency to start RRT early in the course of ARF. As a consequence, most patients who would otherwise be classified as having ARFS are classified as having SARFS. We found the distributions of the RIFLE and Bellomo classifications for ARF to correspond but only weakly, in Kendall's W-test.

6.2. Monocyte human histocompatibility leukocyte antigen-DR (HLA-DR) expression and cytokine plasma levels in pathogenesis of acute renal failure (II)

The results of the Study II demonstrated that monocyte HLA-DR expression and plasma levels of IL-6, IL-8, and IL-10 differ significantly between ARF and

nonARF patients. Monocyte HLA-DR expression was lower and plasma concentrations of IL-6, IL-8, and IL-10 higher in ARF than in nonARF patients on days 2 and 3. On day 1, a significant difference was found in IL-8 and IL-10 plasma concentrations.

The expression of HLA-DR on monocytes was significantly lower in ARF patients than in nonARF patients on days 2 and 3. Generally, low HLA-DR expression on monocytes is considered an anti-inflammatory response, as monocyte HLA-DR expression is needed for antigen presentation for T-cells (Nunez et al. 1987; Cheadle 1993). On the other hand, HLA-DR expression on monocytes is upregulated by pro-inflammatory cytokines, predominantly interferon γ (Donnelly et al. 1990). Previous results on monocyte HLA-DR expression in ARF are sparse. One study reported increased histocompatibility class II protein expression in the interstitium, in collecting tubules, and on periglomerular cells in a rat model of ischemia/reperfusion injury in the kidney (Takada et al. 1997). Another study described lower monocyte HLA-DR expression in sepsis patients than in a heterogeneous ICU population (Lin et al. 1994). However, these results do not contradict the results of the Study II, as the earlier study did not include ARF patients as a subgroup. Despite all patients in the Study II being diagnosed with SIRS/sepsis and their monocyte HLA-DR expression as a group being decreased, the patients with ARF had an even lower monocyte HLA-DR expression.

ARF patients had significantly higher IL-6, IL-8, and IL-10 concentrations than nonARF patients, except for IL-6 concentration on day 1. This is in accord with evidence from a previous study, where increased plasma levels of IL-1β, IL-6, IL-8, IL-10, and TNF-α were observed in ARF patients compared with healthy subjects or patients with end-stage renal disease (Simmons et al. 2004). Furthermore, in rat studies an increase in IL-6 expression and IL-6 gene upregulation after ischemic injury have been found (Takada et al. 1997; Lemay et al. 2000; Kielar et al. 2005). Other studies on interleukin levels in ARF have measured urine levels of IL-6 and IL-8 (Dohi et al. 1991; Smith et al. 2000). One of these studies demonstrated an association between high levels of IL-6 in urine and progression of IgA nephropathy (Dohi et al. 1991). The other found increases in IL-6 and IL-8 in urine during renal transplant rejection (Smith et al. 2000). Support for the central role of cytokines in the pathogenesis of ARF emerged in a study where T-cell-deficient mice developed a less severe kidney dysfunction than wild-type mice after ischemic injury (Burne et al. 2001).

6.3. Cystatin C in diagnosing acute renal failure (III)

Abnormal values of serum cystatin C and plasma creatinine seemed to appear equally quickly in ARF. Serum cystatin C concentrations correlated with plasma creatinine and plasma urea concentrations and showed excellent predictive value for ARF in ROC analysis. One recent study in critically ill patients reported cystatin C to increase almost two days earlier than creatinine in ARF patients (Herget-Rosenthal et al. 2004). This discrepancy in conclusions

may be explained by differences in patient selection. Subjects in Study III were consecutive ICU patients without exclusions, whereas in the study by Herget-Rosenthal et al. several exclusions were made. Their study only included patients with several risk factors for developing ARF. Furthermore, all patients with ARF at admission or at risk for quickly developing severe ARF were excluded. Hence, their patients represented a subgroup of ICU patients that was likely to develop ARF slowly. This design was likely better in detecting small changes in GFR and in testing the sensitivity of markers of kidney function. Study III, by contrast, was aimed at detecting a clinically significant result for the average ICU patient. We cannot therefore rule out a more sensitive nature of cystatin C in detecting ARF in patient subgroups.

In Study III, the increase in serum cystatin C concentration occurred as quickly as the increase in plasma creatinine concentration. The results are in disagreement with two studies in critically ill patients, which determined the ability of serum cystatin C to detect small changes in GFR, measured by creatinine clearance or by the Cockcroft-Gault formula (Delanaye et al. 2004; Villa et al. 2005). In both of these studies, the GFR limit for ARF was set at <80 mL/min/1.73m^2. One of these studies reported that the ability to detect ARF was better with serum cystatin C than with plasma creatinine by ROC analysis (Villa et al. 2005). The other failed to show any difference for serum cystatin C and plasma creatinine in the ROC analysis, but noted that abnormal values of serum cystatin C were seen significantly more often than abnormal values of plasma creatinine in patients with diminished GFR (Delanaye et al. 2004). One recent study, by contrast, is in agreement with the results of the Study III (Mazul-Sunko et al. 2004). In this study serum cystatin C did not associate with ARF in critically ill patients with sepsis.

Treatment with corticosteroids had no effect on serum cystatin C concentrations in ARF patients. However, in nonARF patients, increased serum cystatin C concentrations were found during corticosteroid treatment. Previous results on the subject are contradictory. One study demonstrated a dose-dependent increase in cystatin C concentrations during corticosteroid treatment (Risch et al. 2001). However, the dose of corticosteroid treatment in this study was larger than in ours, and the patients also received treatment with cyclosporine A and azathioprine. Two studies in children present contrary results, where corticosteroid treatment had no effect on cystatin C concentrations (Bökenkamp et al. 1998; Foster et al. 2006).

6.4. Prevention and treatment of acute renal failure in rhabdomyolysis (IV)

The results of the Study IV demonstrated that clearing myoglobin from plasma is possible using HDF. Approximately 60 mg of myoglobin was found in the ultrafiltrate after four hours of HDF. Myoglobin clearance was about 50 mL/min, and the sieving coefficient for myoglobin was 0.31. The results are in accordance with evidence from previous studies on myoglobin clearance during continuous hemofiltration (Nicolau et al. 1996; Amyot et al. 1999). In an animal

model of rhabdomyolysis-induced ARF treated with continuous arteriovenous hemofiltration (CAVH), the amount of myoglobin filtrated in six hours was around 400 mg. In a case report of a patient with a very high plasma myoglobin concentration, the amount of myoglobin removed in 16 h of continuous venovenous hemofiltration (CVVH) was around 700 mg (Amyot et al. 1999). Continuous venovenous hemodiafiltration (CVVHDF), on the other hand, has not been shown to increase plasma myoglobin clearance (Mikkelsen et al. 2005). One explanation might be that CVVHDF was started because of ARF and was not aimed solely at clearing myoglobin (Mikkelsen et al. 2005).

The reduction of plasma myoglobin during four hours of forced alkaline diuresis in Study IV was around 15% of the baseline concentration. This is consistent with the few previous studies available, where the daily disappearing rates of myoglobin in rhabdomyolysis patients without ARF have been reported as 43% and 62% (Wakabayashi et al. 1994; Mikkelsen et al. 2005). In the present study, the myoglobin elimination rate without urine alkalization was not measured, which makes calculation of the effect of urine alkalization on myoglobin baseline elimination rate impossible. One study has demonstrated that myoglobin clearance via kidneys is low, only 3 mL/min (Lappalainen et al. 2002). This suggests that the increase in myoglobin clearance by urine alkalization is small. Thus, the decrease in myoglobin concentrations observed in our study probably reflects the baseline metabolic rate of myoglobin.

The results of the Study IV indicate that compared to the conventional treatment of rhabdomyolysis with FAD the elimination of myoglobin is faster when HDF is added to the treatment. In Study IV, the percentual decrease in myoglobin concentration was significantly greater during HDF than during FAD alone. The mean additional removal of myoglobin with HDF was around 6000 µg/L (95% CIs 300-12000 µg/L).

6.5. Mortality in acute renal failure (I-III, V)

Short-term mortality (I-III)

The overall short-term mortality rate among critically ill patients with ARF was 30%, varying from 20% (Studies I-II) to 48% (Study III). The short-term mortality rate was relatively low compared with the mortality rates presented in several other studies on ARF patients (Uchino et al. 2005; Ympa et al. 2005). Remarkably, the 28-day mortality rate in ARF patients with SIRS/sepsis was only 22%. This may be explained by the majority of ARF patients not having sepsis despite having SIRS. Only 22% of SIRS patients with ARF were actually diagnosed with sepsis. In patients without ARF, the overall hospital mortality rate of 13% was significantly lower than that in patients with ARF.

In the Study I, hospital mortality increased as the severity of ARF increased (graded according to RIFLE and Bellomo scores). This is in accordance with previous results, where the severity of renal dysfunction has been found to correlate with mortality (Kellum et al. 2002; Abosaif et al. 2005; Bell et

al. 2005; Ostermann et al. 2005). Regarding hospital mortality, sensitivity was better with the RIFLE classification and specificity with the Bellomo classification. Both classifications showed good sensitivity for death in the least severe stage of ARF (either Risk or ARI) and good specificity for death in the most severe stage (either Failure or SARFS).

The observed short-term mortality of ARF patients was comparable with or higher than the short-term mortality of other critically ill patients reported previously. Two large studies on ICU patients documented significantly lower hospital mortalities in heterogeneous ICU populations: 12% (Zimmerman et al. 1998) and 10% (Niskanen et al. 1996). However, a recent meta-analysis reported higher hospital mortality rates in a heterogeneous ICU population: between 11% and 64% (Williams et al. 2005).

Long-term mortality (V)

Based on the results of the Study V, the long-term mortality of ARF patients treated with RRT is high, although it slows down with time. After hospital discharge, an additional mortality of 20% occurred during the first year. An additional mortality of 10% of patients occurred over the next four years, resulting in a total 5-year mortality of 70%. Outcome was independent of treatment year, increasing the reliability of the Kaplan-Meier estimates of survival for patients with different follow-up times. The results are in accord with those of several previous studies, which have all documented the mortality rate to be extremely high at the beginning of illness, but then to slow down (Gopal et al. 1997; Korkeila et al. 2000; Morgera et al. 2002; Bell et al. 2005; Luckraz et al. 2005). One previous Finnish study documented mortality rates very similar to ours. In their study, the mortality of ARF patients was 55% at 6 months and 65% at 5 years (Korkeila et al. 2000). Another recent study with 207 ARF patients treated with CRRT reported the mortality rate to be 55% already at 60 days and the 6-month mortality rate was higher; 60% (Bell et al. 2005). In cardiopulmonary bypass patients requiring RRT for ARF postoperatively, the long-term mortality was fairly low; 1- and 5-year mortality rates were 47% and 48%, respectively (Luckraz et al. 2005). A higher 6-month mortality rate of 73% has been reported in a study of 490 ARF patients treated with RRT (Hamel et al. 1997).

Comparison of the long-term mortality of ARF patients with the mortality of other ICU patients reveals that mortality of the former ARF patients remains higher several years. A Finnish study has demonstrated the long-term mortality of heterogeneous ICU patients to be 36% at 1 year, 48% at 5 years, and 51% at 6 years (Kaarlola et al. 2003).

6.6. Prediction of hospital mortality in acute renal failure (I-III)

Scoring methods for severity of illness (I)

1. ARF-SPECIFIC SCORING METHODS (I)

The maximum RIFLE score for the first three days in the ICU was found to be an independent predictor of hospital

mortality in the Study I. Previous studies on the subject are few (Abosaif et al. 2005; Ostermann et al. 2005). Recently, a single study proposed that the RIFLE score would improve the predictive ability of general severity-of-illness scores in ARF patients (Abosaif et al. 2005). However, this study had several major limitations: the study population was selected, ICU mortality instead of hospital mortality was evaluated, and the statistical analysis was flawed due to inadequate ROC and logistic regression analyses. In Study I, the Bellomo classification did not predict hospital mortality independently. This contradicts one previous study on the subject, which found all three stages of the Bellomo classification to be independent predictors of hospital mortality (Ostermann et al. 2005). This difference in results might be explained by differences in study populations. In the study by Ostermann et al., nearly 20% of survivors and over 30% of nonsurvivors were reported to have an underlying chronic end-stage disease, and the mortality rates were higher, although the APACHE II scores did not differ.

While the RIFLE classification was found to be an independent predictor of hospital mortality, its power in discriminating between survivors and nonsurvivors was only moderate, and the discriminative power of the Bellomo classification was similar. These findings are in line with the results of a recent large study that evaluated four ARF-specific scoring methods and described their discriminative powers for mortality as moderate (Uchino et al. 2005). The difference between the RIFLE and Bellomo classifications, and the scores by Liano et al. (1993), Chertow et al. (1998), Mehta et al. (2002), and Paganini et al. (1996) is that the first two focus on scoring the severity of ARF, whereas the latter four score the general severity of illness in ARF patients. The results suggest that ARF-specific severity-of-illness scoring methods in general tend not to perform ideally as predictors of mortality in heterogeneous ICU population. However, in Study I, the maximum RIFLE score for the first three days in the ICU proved to be an independent predictor of hospital mortality, indicating that the RIFLE score may be suitable for classification of ARF patients in clinical mortality studies.

2. General severity-of-illness scoring methods (I-III)

The two general severity-of-illness scores, the APACHE II score and the SOFA score, performed well as predictors of mortality in these studies. They were both found to be independent predictors of short-term mortality in this large heterogeneous ICU population (Studies I-III combined). This finding is in agreement with earlier studies, where APACHE II and SOFA score have predicted mortality in ARF patients with AUCs of 0.747-0.878 and 0.868, respectively (van Bommel et al. 1995; Brivet et al. 1996; Parker et al. 1998; de Mendonca et al. 2000; Chen et al. 2001). The discriminative power concerning short-term mortality for APACHE II and SOFA scores ranged from moderate to good in Studies I-III. Previous studies on the subject show divergence. In ARF patients and in a general ICU population, the discriminative power for mortality has been reported as excellent for the day

1 SOFA score (Janssens et al. 2000; Mehta et al. 2002), in a heterogeneous ICU population as good, with an AUC of 0.776 (Pettilä et al. 2002), and in end-stage renal disease patients in the ICU as moderate (Dara et al. 2004).

Laboratory tests (II, III)

1. Serum concentrations of interleukins 6, 8, and 10 (II)

While Study II demonstrated significantly higher IL-6 and IL-8 plasma concentrations in ARF patients than in nonARF patients, ROC analysis and logistic regression analysis failed to demonstrate any reliable benefit in outcome prediction for IL-6 and IL-8. ROC analysis showed moderate predictive power of only day 2 plasma levels of IL-6 and IL-10, and logistic regression analysis revealed that admission plasma IL-8 level, although not an independent variable, was second to APACHE II score in predicting mortality. Previous studies on this subject show great diversity. High IL-10 plasma levels have been found in nonsurvivors among sepsis patients (Gogos et al. 2000) and among patients with meningococcal disease (Lehmann et al. 1995). One recent study with 98 ARF patients determined the plasma concentrations of exactly the same interleukins that were examined in Study II and observed significantly higher plasma levels of these interleukins in nonsurvivors than in survivors (Simmons et al. 2004). For each natural log unit rise in interleukin levels, they found the odds for death to rise accordingly, and concluded that the plasma levels of IL-6, IL-8, and IL-10 predict mortality in ARF patients. However, in logistic regression analysis with APACHE II score included, the only independent predictor of 28-day mortality was IL-6 (measured at the time of nephrology consultation). In one previous study reporting results similar to ours, IL-8 plasma levels, but not IL-6 plasma levels, were found to predict mortality (Friedland et al. 1996). However, in neither of these studies was the ability of interleukins to predict mortality measured by ROC analysis, as has been recommended (Ruttimann 1994); the studies merely reported an association between high interleukin levels and increased mortality.

2. Monocyte HLA-DR expression (II)

The results of this study showed no discriminative power in predicting mortality for monocyte HLA-DR expression by ROC analysis. This is in contrast to earlier studies, where low monocyte surface expression of HLA-DR has been associated with increased mortality in sepsis (Volk et al. 1996; Tschaikowsky et al. 2002). However, results have also documented no association between low monocyte HLA-DR expression and mortality (Perry et al. 2003).

3. Serum cystatin C concentration (III)

In ROC analysis, the ability of serum cystatin C to discriminate between survivors and nonsurvivors in Study III was poor, although it was slightly better than that of plasma creatinine. However, forward stepwise multiple logistic regression analysis revealed that admission serum cystatin C

concentration was not an independent predictor for hospital mortality but that plasma creatinine concentration was. Serum cystatin C is therefore not clinically useful in predicting mortality of ARF patients.

6.7. Quality of life after acute renal failure (V)

Based on the results of Study V, the HRQoL of former ARF patients is lower than that of the age- and gender-matched general population. Their quality-adjusted survival, measured by quality-adjusted life-years (QALYs), is also inferior to other groups of critically ill patients (Angus et al. 2001). However, the patients are as satisfied with their health as the general population.

Health-related quality of life (V)

The answers of the former ARF patients to the EQ-5D questionnaire revealed that their HRQoL was significantly lower than that of the age- and gender-matched general population. The results are in accord with previous studies on the HRQoL after critical illness. A recent systematic review of 21 selected independent studies (out of a total of 8894 studies) with altogether 7320 patients concluded that the HRQoL of ICU survivors is lower than that of the general population (Dowdy et al. 2005). However, some earlier studies on ARF patients have reported a fairly good HRQoL after ARF (Gopal et al. 1997; Korkeila et al. 2000; Maynard et al. 2003). One of these studies evaluated 62 former ARF patients by the Nottingham Health Profile six months after discharge and described HRQoL after ARF to be good (Korkeila et al. 2000). In their study, most impairment was found in overall energy and the physical domain of HRQoL. Another study using the Nottingham Health Profile also reported impairments in mobility and energy in 35 former ARF patients (Gopal et al. 1997). Furthermore, they reported physical pain, interrupted sleep, and depression to be common after a follow-up of 2.5 years. However, the validity of the results of both of these studies is compromised by the fact that the patients were not compared with the general population. Comparison of ARF patients' HRQoL with that of the general population has been done earlier only in a small study of 12 patients (Maynard et al. 2003). Contrary to our results, they found patients' mental health to be comparable with and their physical health to be only slightly poorer than that of the general population, as measured by the Short Form Health Survey (SF-36) six months after discharge.

Study V also evaluated patients' perceived health by the VAS score. The results showed no clinically significant difference between former ARF patients and the age- and gender-matched general population. Evaluation of VAS scores in three separate age groups revealed a connection between age and perceived health. In older age groups, perceived health was increasingly similar between patients and their age- and gender-matched peers. Whether this finding reflects diminishing general health in older people or younger patients' greater expectations of health, or both, is unclear. The finding is consistant with a previous study on ICU patients, which had demonstrated improved perceived

health status following ICU treatment in the elderly (Konopad et al. 1995).

The results of Study V are in agreement with previous findings (Gopal et al. 1997; Morgera et al. 2002; Maynard et al. 2003). The earliest of these studies reported that the majority of 35 former ARF patients were satisfied with their health after a follow-up time of 2.5 years (Gopal et al. 1997). Another study with 267 former ARF patients treated with CRRT described patients' current health to be good or excellent for 77% of respondents (Morgera et al. 2002). The results of a small study of 12 patients showed that the majority of patients rated their health as "good" or "fair" 6 months after discharge (Maynard et al. 2003). None of the patients in that study rated their health as "excellent", and 25% rated it as "poor".

Costs of hospital treatment (V)

Based on the results of Study V, the costs of hospital treatment per quality-adjusted life-years (QALYs) in ARF patients treated with RRT were high. This was due not only to the high cost of treatment but also to the poor quality-adjusted survival of these patients. Costs of RRT were 25 000 €, and total costs of hospital treatment were approximately 222 000 € /QALY. This was higher than the 50 000-100 000 € limit usually considered acceptable in the literature (Lee et al. 1996; Hamel et al. 1997; Angus et al. 2001, 2003). These results are in agreement with previous studies, which have demonstrated the total costs of treating patients with ARF to be high (Hamel et al. 1997; Korkeila et al. 2000; Sznajder et al. 2001). A recent Finnish study found the total costs of treating ARF to be around 80 000 € / 6-month survival (Korkeila et al. 2000). This study did not take into account the effect of quality-adjusted survival, which means that the total costs of treatment / QALY calculated from results is actually similar to ours. Another study with 490 patients treated with RRT described the overall costs of treatments to be around 130 000 $ (103 000 €) /QALY (Hamel et al. 1997). The costs per QALY in that study depended on the patients' outcome category and ranged from 60 000 $ (48 000 €) to 270 000 $ (214 000 €) /QALY. The highest costs / QALY were noted in patients with the worst outcomes. However, much lower costs per QALY have also been reported. One study found the total cost of hospital treatment of ARF patients to be around 30 000 $ (24 000 €), but they also reported that ARF patients had the highest costs of treatment / QALY of all intensive care patients (Sznajder et al. 2001).

6.8. Limitations of the study

Several limitations of these studies should be addressed. First, the optimal timing for evaluation of mortality associated with ARF is not clear. In studies I-III, hospital mortality was evaluated ignoring some of the later ARF-related mortality. In Study V, where the long-term mortality was evaluated after a median of approximately four years, the reported ARF-related mortality rate was probably overestimated.

Second, the general severity-of-illness scores have originally been validated using manual data collection. However, collection of data here was

mainly based on a computerized system. Computerized data collection has previously been shown to result in more frequent measurements, to increase the probability of detecting abnormal values, and to produce higher severity-of-illness scores (Suistomaa et al. 2000). In their study, where bias was reported, computerized data collection resulted in worse predictive power for mortality (Suistomaa et al. 2000). Hence, if any bias had occurred in our study, it would have been in favor of a less significant result.

Third, in Studies II and III, the effect of continuous hemodiafiltration on the plasma cytokine levels and serum cystatin C levels could not be assessed. However, previous studies have failed to prove any clinically significant decrease in serum cytokine concentrations during continuous hemodiafiltration (Kellum et al. 1998; Suzuki et al. 2002). To date, the exact clearance rate of cystatin C during RRT is still unclear (Thysell et al. 1988; Kabanda et al. 1994; Tian et al. 1997; Campo et al. 2004). In Study III, a decrease in serum cystatin C concentrations was seen in ARF patients over time, whereas plasma creatinine concentration simultaneously increased. These results suggest that differences exist in RRT clearance rates of these markers or in their elimination half-lives.

Fourth, no prior study data were available to be used as reference values in the power analysis in Study IV, which means that the values used in the power analysis were approximations derived from clinical experience. The appropriate sample size was calculated with approximated decreases in myoglobin concentration during the treatments. For HDF, the decrease was assumed to be around 12 000 µg/L, and for FAD around 6000 µg/L, with a standard deviation for the difference of 6000 µg/L. However, the observed decreases in plasma myoglobin concentration were smaller than those anticipated in the power analysis. The mean plasma myoglobin decrease during HDF was around 10 000 µg/L, and during FAD around 4000 µg/L. Hence, the power analysis resulted in a sample size that was probably too small to reveal a statistically significant decrease in plasma myoglobin concentration during HDF. Thus, the maximal effect of HDF on myoglobin elimination that we could demonstrate was approximately 12 000 µg/L in four hours.

Fifth, the optimal follow-up for measuring HRQoL after critical illness is still unclear. In a longitudinal study with repeated HRQoL measurements, significant improvement in HRQoL occurred during the post-discharge period as late as several years after discharge (Pettilä et al. 2000; Kaarlola et al. 2003). On the other hand, a long period between hospital discharge and HRQoL measurement allows other significant life events to affect the HRQoL. Furthermore, information about patients' pre-ICU HRQoL could not be obtained in Study V, and hence, no comparison between pre- and post-ICU data was made. This may have influenced the results since patients' previous health state has been shown to affect the HRQoL after treatment (Ridley et al. 1997; Granja et al. 2002).

Finally, in Study IV, treatment with FAD was not completely successful, as mean urine pH during treatment was 6.2 and a statistically non-significant trend towards a higher median hourly diuresis

in group B than in group A was seen. However, previous studies have suggested that GFR does not affect myoglobin clearance rate (Lappalainen et al. 2002). Since urine pH and GFR have an effect on myoglobin toxicity in renal tubular cells, not on myoglobin clearance rate, the results were likely not confounded by the shortcomings of FAD.

6.9. Clinical implications

Several clinical implications are proposed based on the results of Studies I-V.

Although mortality of ARF patients is high, the highest mortality rate occurs during hospitalization. With time, the mortality rate slows down. After a period of approximately six months to one year, the mortality rate reaches that of other ICU patients. These patients who survive are fairly content with their quality of life after ARF. Patients with the potential to survive thus seem to benefit from adequate treatment. Adequate treatment is, however, more expensive than the generally accepetd cost-effective figure of 50 000-100 000 € (Lee et al. 1996; Angus et al. 2001; Angus et al. 2003). Evidence suggests that to be effective the treatment should be started early and at a sufficient dose. This leads to the conclusion that in order to be able to provide adequate treatment to those able to benefit from it we need to be able to predict which patients will survive. Our ability to do this is, however, limited. Based on our results, APACHE II and SOFA scores are still the best predictive tools for outcome in critical care patients. To date, no ARF-specific scoring method with good predictive power for mortality exists. Whether the new consensus definition for ARF, the RIFLE definition, can be used in combination with the APACHE II score or the SOFA score to increase predictive power remains to be elucidated.

As a marker of renal dysfunction, plasma creatinine concentration maintains its superior ranking. However, we found serum cystatin C to be as good as plasma creatinine in detecting ARF or predicting patient survival. It may even prove to be more sensitive than plasma creatinine in certain subgroups of patients. This especially applies to patients whose muscle mass is abnormal or in whom renal failure develops slowly. Finally, daily measurement of plasma cytokine concentrations or monocyte HLA-DR expression is unlikely to have a clinical application in critically ill patients with ARF.

HDF can be used to clear myoglobin from the plasma. The clinical significance of this is, however, unclear. Even today, little is known about the effect FAD has on myoglobin elimination rate. The low success rate of FAD in this study is also often seen in clinical practice. On the other hand, HDF is more expensive and laborious than FAD. Therefore, treatment of rhabdo-myolysis should be started with FAD. If urine alkalization is unsuccessful or the patient develops a need for RRT for ARF or for fluid overload, RRT with filtration techniques should be considered.

6.10. Future perspectives

As a whole, ARF has been studied extensively over the past decades. Abundant research on different prevention and treatment strategies,

possible renal function markers, and tools for outcome prediction exists. Despite many promising ideas, some basic questions remain unanswered.

To date, the lack of a globally accepted definition for ARF complicates comparison of results between studies. As a consequence, drawing conclusions from systematic reviews and meta-analyses on ARF is difficult, and guidelines for clinical practice are therefore somewhat uncertain. The RIFLE definition, which in this study seemed more promising than the Bellomo classification, is based on a consensus idea and has not been properly validated. In future, a large multinational study focusing on outcome is needed for the validation.

An ideal marker of renal function needs to be produced at a constant rate in all age groups, should only be eliminated via the kidneys, and should neither be secreted nor reabsorbed in the tubules. Cystatin C appeared to be such a marker, but closer examination revealed that it does not perform as well in ARF as in chronic renal failure. Now other low molecular weight proteins, such as β-2-microglobulin (Bianchi et al. 2001; Paskalev et al. 2001; Mojiminiyi et al. 2003) and tumor-associated trypsin inhibitor (Tramonti et al. 2003), are being tested for their ability to function as markers of renal function. N-terminal prohormone of proatrial natriuretic peptide has been investigated as a potential marker of renal function, but studies of its accuracy in ARF are sparse (Mazul-Sunko et al. 2004). Another recently proposed marker of renal function is 2-(α mannopyranosyl)-L-tryptophan (Takahira et al. 2001). Calcium-binding proteins have also been suggested as markers of tubular injury and recovery (Cheng et al. 2005). Furthermore, a multitude of potential new markers for renal function have recently been proposed in animal studies. However, further studies are needed in order to find an accurate marker for renal function in ARF.

Different treatment methods for ARF have been examined widely. Several new potential therapies require further evaluation. As recently reviewed by Vesely (2006) the vessel dilator peptide, located within the atrial natriuretic peptide (ANP) prohormone, has shown promising results in humans. Prevention and treatment of radiocontrast media-induced ARF have also been extensively investigated. However, no clear findings have emerged, and thus, more studies are needed. Even the efficiency of N-acetylcysteine (NAC) in prevention of radiocontrast medium-induced ARF is still under debate, although several meta-analyses already exist on the subject (Kshirsagar et al. 2004; Zagler et al. 2006). More studies are also warranted on the effect of theophyllin in preventing ARF and mortality after exposure to radiocontrast media. In one study, isotonic sodium bicarbonate was reported as more effective in preventing contrast media-induced ARF than sodium chloride (Merten et al. 2004). In recent animal studies, several substances have shown promising results in reducing ischemic injury; these include ethyl pyruvate (Miyaji et al. 2003), erythro-poietin (Patel et al. 2004), apotransferrin (de Vries et al. 2004), diallyl sulfide (Pedraza-Chaverri et al. 2003), choles-terol-lowering drugs (Yokota et al. 2003), endotelin receptor antagonists (Huang et al. 2002), and propionyl-L-

carnitine (Mister et al. 2002). Interstingly, first animal studies on stem cell therapy in ARF have also been conducted (Kale et al. 2003; Morigi et al. 2004).

The number of ARF patients in one ICU is relatively low and obtaining large study populations requires combining patient material from several ICUs. However, in general, the number of multinational multicenter studies on ARF is low (Uchino et al. 2004; Uchino et al. 2005; Uchino et al. 2005). Large studies on ARF, similar to those that exist on sepsis (Moreno et al. 1999; Angus et al. 2004; Laterre et al. 2004) and acute myocardial infarction (Webb et al. 2001; Goldberg et al. 2004; Reed et al. 2005; Kauf et al. 2006), are needed.

Studies on long-term outcome of ARF patients in particular, are sparse (Druml 2005; Radhakrishnan et al. 2006), and this topic warrants more thorough coverage. Another area for elucidation is the cost-effectiveness of treating ARF (Hamel et al. 1997; Korkeila et al. 2000; Angus et al. 2001).

7. CONCLUSIONS

Based on the results of these studies, the following conclusions can be drawn:

1. According to two newly proposed scoring methods for ARF, the RIFLE and the Bellomo classifications, increasing severity of renal dysfunction is associated with increasing hospital mortality in critically ill patients.

2. In critically ill patients with SIRS, monocyte HLA-DR expression is significantly lower and plasma levels of IL-6, IL-8, and IL-10 significantly higher in those with ARF than in those without ARF. Serum cystatin C levels are significantly higher in critically ill patients with ARF than in patients without ARF. Serum cystatin C seems to be as good as plasma creatinine in detecting ARF in critical care patients. In acute renal dysfunction, abnormal values of serum cystatin C and plasma creatinine appear equally quickly.

3. HDF can be used to clear myoglobin from plasma, which may hinder the development of ARF in rhabdomyolysis.

4. The outcome of patients with ARF is poor. Both short- and long-term mortalities are high. The HRQoL of those who survive is lower than that of the age- and gender-matched general population. However, these patients are as satisfied with their health as the general population.

5. The ability of ARF-specific severity-of-illness scores (the RIFLE and Bellomo scores) to predict hospital mortality is only moderate. Monocyte HLA-DR expression, plasma concentrations of IL-6, IL-8, and IL-10, and serum cystatin C are not clinically useful in predicting mortality of ARF patients.

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